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ACTA PÆDIATRICA

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FROM THE PEDIATRIC CLINIC OF KAROLINSKA INSTITUTET, NORRTULL'S HOSPITAL. CHIEF: PROF. A. WALLGREN

The Effect of Adrenocorticotropic Hormone (ACTH) on the Circulating Eosinophils in Infants

by

C. G. BERGSTRAND, B. HELLSTRÖM and **B. JONSSON**

It is wellknown, that during the latter part of foetal life and the first part of extrauterine life the adrenal cortex in man undergoes great morphological changes, and that during the neonatal period the adrenal gland loses about half of its weight. The newborn infant shows a great lability in water-salt metabolism, has a tendency to hypoglycemia and has less general resistance than older children and adults. On the basis of these facts, the possibility of a hypofunction of the adrenal cortex in the newborn was quite logically suggested (JAUDON 1950). No real proof of cortical insufficiency in either the full-term or premature baby seems, on the other hand, to have been presented.

It is thus of interest to study the response of the eosinophil leukocytes to adrenocorticotropic hormone. Knowledge of this response, based on a test introduced 1948 by THORN and his collaborators, is considered as a valuable aid in the diagnosis of adrenal cortical insufficiency. 25 mg of adrenocorticotropic hormone (ACTH) given to normal individuals in a single dose results in a drop in the eosinophil count of 50 % or more in 4 hours. Patients with Addison's disease show no or very little response.

The purpose of the present investigation has been to study the response of the eosinophils to ACTH in premature and full-term newborn infants compared with older infants. Further the normal variation in the number of eosinophil leukocytes have

been studied over a four hour period. In a few cases the effect of cortisone on the eosinophils of infants has been studied.

Methods

For counting the eosinophil leukocytes RUD's modification of the Dunger method was used. The eosinophils are stained with a solution of Magdala red in aceton and water and counted directly in a counting chamber. This method gives reliable results for capillary blood, provided certain precautions are taken (BERGSTRAND *et al.*, 1950). The blood was diluted 1:20, and the cells were counted in a Jessen chamber with a depth of 0.4 mm and a volume of 10 cmm. The amount of undiluted blood examined was 1 cmm.

The eosinophils were counted at 8 a. m. and at noon. (In a few cases the determinations were made at 9 a. m. and 1 p. m.)

The adrenocorticotropic hormone of the Organon company, "*Cortrophin*", was used.[1] Originally it was planned to use only ACTH of the same batch, but, as sufficient amounts could not be supplied, several batches were used. The dose of ACTH was calculated on the basis of body weight. Doses of $^1/_3$ mg/kg, $^2/_3$ mg/kg and in a few cases $^4/_3$ mg/kg ACTH were used, corresponding to a dose in adults of 25, 50 and 100 mg. The ACTH was injected intramuscularly in the buttock or in the thigh.

"*Cortisone*" (cortone acetate, Merck company) was given intramuscularly in a dose of 5 mg per kilogram body weight.

The injections were given immediately after the first blood specimens had been taken.

Material

The spontaneous variations in the number of eosinophils at 8 and 12 o'clock were studied in 49 full-term newborns (0—7 days old) and in 26 older infants (30—120 days old). The same variation in prematures were studied, 19 of them newborns (0—7 days old) and 9 of them older.

The effect of ACTH on the number of circulating eosinophils was investigated in three groups of healthy infants. The first group included 54 newborn (0—7 days old) full-term infants. Of these, 24 received $^1/_3$ mg ACTH per kilogram bodyweight, 23 received $^2/_3$ mg and 7 received $^4/_3$ mg. The second group consisted of 38 older infants (30—120 days old). Of these infants 6 cases received $^1/_3$ mg and 32 received $^2/_3$ mg per kilogram bodyweight.

The effect of cortisone was studied only in 9 newborn (0—7 days old) babies and in 20 infants 30—120 days old.

[1] Kindly supplied by courtesy of dr. F. Paulsen.

Results

Full-term Babies. The main results are shown in the diagrams. Fig. 1 shows the spontaneous change in the number of eosinophils from 8 to 12 o'clock in 49 *newborns*. When the deviation of the number of eosinophils at 12 o'clock is expressed in per cent of the number at 8 o'clock, the mean value of this deviation is 0.2 % with a standard error of the mean of 3.2. As seen from the figure, however, the range is rather wide, and in a few cases this spontaneous variation exceeds 50 %. The mean value for the number of eosinophils in 49 full-term newborns at 8 o'clock is 471 per cmm with a standard error of the mean of 45.5.

The second diagram shows the change in the number of eosinophils in these full-term *newborn* infants from 8 o'clock when ACTH is given in a dose of 1/3 mg, 2/3 mg and 4/3 mg per kilogram bodyweight to 12 o'clock.

With the 1/3 mg dose (24 cases) the mean value of the decrease is 32.7 per cent ± 4.0, which is highly significant ($t = 8.2$, 23 degrees of freedom, corresponding to $p < 0.001$) The 2/3 mg dose (23 cases) gave a decrease of 23.8 ± 2.9 which is also highly significant ($t = 8.2$, 22 degrees of freedom, corresponding to $p < 0.001$). The difference in the decrease after the 1/3 mg dose and the 2/3 mg dose is -8.9 ± 4.9, i. e. not significant. The change in the number of eosinophils after 4/3 mg per kilogram bodyweight was only investigated in 7 full-term newborns. The mean value for the decrease with that dose is 34.0 per cent.

The difference between the spontaneous change in the number of eosinophils in full-term newborns from 8 to 12 o'clock and the change induced after 1/3 mg ACTH per kilogram bodyweight is $-0.2 - (-32.7) = 32.9 \pm 5.0$ which is highly significant ($p < 0.001$). The same difference when the 2/3 mg dose was used is $0.2 - (-23.8) = 24.0 \pm 4.3$, which is also highly significant ($p < 0.001$).

The spontaneous change in the number of eosinophils from 8 to 12 o'clock in 26 *older* full-term infants (30—120 days old) is illustrated by the third diagram (fig. 3). The mean value of this change is -7.3 per cent ± 5.0.

The mean value for the number of eosinophils at 8 o'clock in

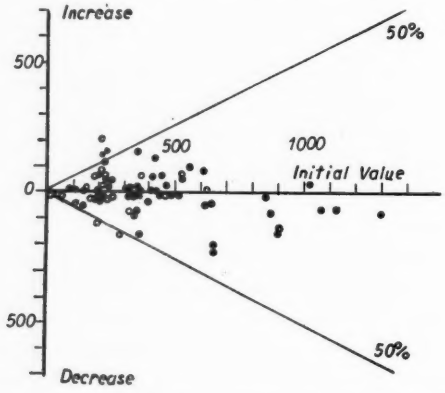

Fig. 1. Spontaneous change in the number of eosinophils from 8 to 12 o'clock in infants. 0—7 days old. ○ = prematures. ● = fullterm infants.

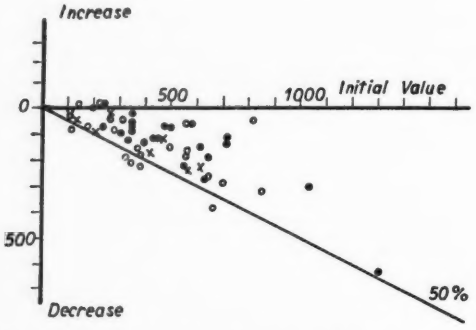

Fig. 2. The change in the number of eosinophils in full-term infants 0—7 days old after injection of $^1/_3$ mg (= ○), $^2/_3$ mg (= ●) and $^4/_3$ mg (= ×) ACTH per kilogram bodyweight.

these older full-term infants is 412 per cmm with a standard error of the mean of 46.9.

The effect of ACTH in a dose of 1/3 and 2/3 mg per kilogram bodyweight as judged by the decrease in circulating eosinophils in these older infants (30—120 days old) is shown in fig. 4. The mean value of the decrease after 1/3 mg/kg is 41.2 per cent but

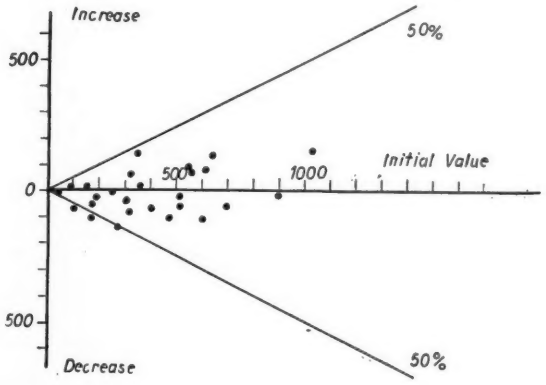

Fig. 3. Spontaneous change in the number of eosinophils from 8 to 12 o'clock in full-term infants 30—120 days old.

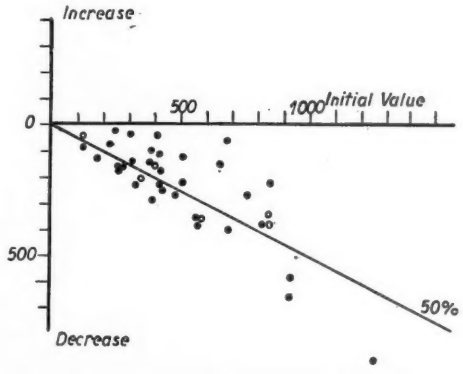

Fig. 4. The change in the number of eosinophils in full-term infants 30—120 days old after injection of 1/3 mg (= ○) and 2/3 mg (= ●) ACTH per kilogram bodyweight.

was only investigated in 6 cases. The mean value of the decrease after 2/3 mg/kg (32 cases) is 45.2 per cent $\pm$3.6, a highly significant decrease ($p < 0.001$).

The number of children given the 1/3 mg-dose was to small to allow a statistical analysis, but the result obtained does not point

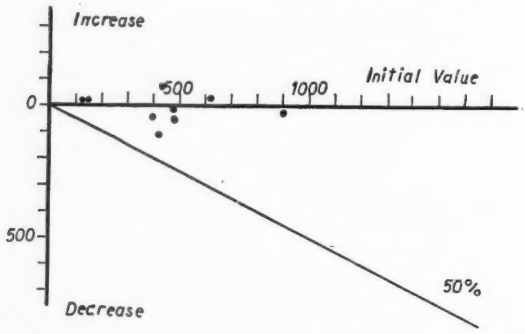

Fig. 5. The effect on the number of eosinophils of 5 mg cortisone per kilogram bodyweight in full-term infants 0—7 days old.

to any difference in the effect between this dose and the dose of 2/3 mg/kg.

The difference between the spontaneous change in the number of eosinophils from 8 to 12 o'clock and the change induced by the 2/3 mg dose of ACTH in these older full-term infants is $-7.3-(-45.2)=37.9\pm6.2$, which is highly significant ($p<0.001$).

The difference between the decrease in the number of eosinophils from 8 to 12 o'clock induced by the 2/3 mg dose of ACTH in older infants (45.2 per cent) and newborns (23.8 per cent) is 21.4 ± 4.5, which is highly significant. In this difference is, however, included the error of the possibly greater spontaneous decrease of the older infants. If this source of error is taken into account and the two groups of infants are then compared, the difference is only 13.9 ± 7.5, which is not significant.

The results with cortisone are given in diagrams 5 and 6. The change in the number of eosinophils from 8 to 12 o'clock after a dose of 5 mg cortisone/kg bodyweight was only investigated in 9 full-term babies 0—7 days of age (Fig. 5). The mean value is +0.7 per cent. The corresponding mean value for 20 infants 30—120 days old is —4.4 per cent ±10.0, a change which is not significant. (Fig. 6).

Premature Babies. The spontaneous change in the number of eosinophils from 8 to 12 o'clock in 19 prematures 0—7 days old is

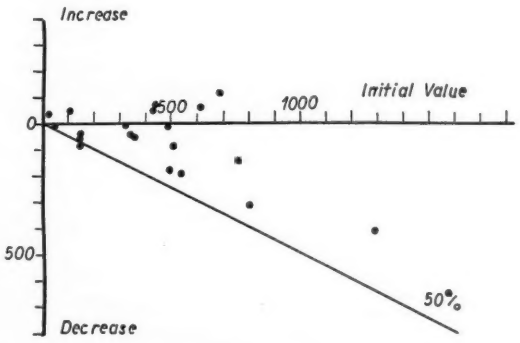

Fig. 6. The effect on the number of eosinophils of 5 mg cortisone per kilogram bodyweight in full-term infants 30—120 days old.

shown in the first diagram. The mean value for this change is $+0.3 \pm 8.7$. This change was also investigated in older prematures (30—120 days old), but as only 9 cases were examined no statistical analysis was made. The mean value is +3.7 per cent.

The mean value for the number of eosinophils per cmm at 8 o'clock in the newborn prematures (19 cases) is 285 with a standard error of the mean of 75.9.

The change in the number of eosinophils in 21 *newborn* (0—7 days old) prematures from 8 to 12 o'clock after an injection of 2/3 mg ACTH per kilogram bodyweight has a mean value of -33.1 ± 4.9, which is highly significant ($t = 6.8$, 20 degrees of freedom, corresponding to $p < 0.001$).

The difference between the spontaneous change in the number of eosinophils from 8 to 12 o'clock (Fig. 1) and the change after the 2/3 mg dose of ACTH per kg is $0.3 - (-33.1) = 33.4 \pm 10.0$, which is highly significant ($p < 0.001$).

An attempt was made to correlate the decrease of the eosinophils in prematures after an injection of the 2/3 mg dose per kg of ACTH with the weight and with the age of the infant (diagrams 7 and 8). No such correlation were found. The coefficient of correlation with weight is -0.05 ± 0.14 and that with age is -0.03 ± 0.14.

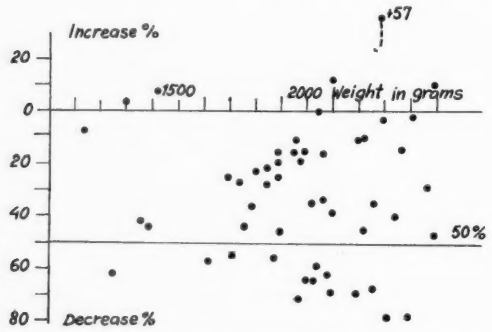

Fig. 7. Correlation between weight in grams/100 and decrease in eosinophils after 1/3 mg (= ○) and 2/3 mg (= ●) ACTH per kilogram bodyweight in premature infants.

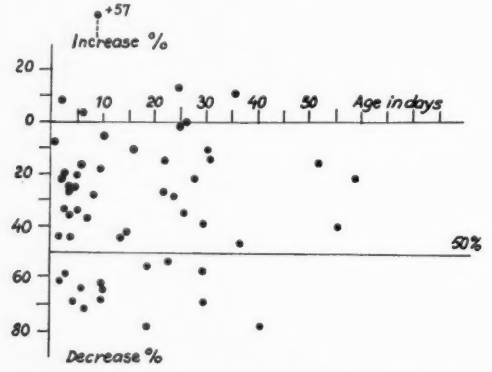

Fig. 8. Correlation between age in days and decrease in eosinophils after 1/3 mg (= ○) and 2/3 mg (= ●) ACTH per kilogram bodyweight in premature infants.

Discussion

It is evident from the results of this investigation that administration of small amounts of ACTH (1/3 and 2/3 mg per kilogram bodyweight) decreases the number of circulating eosinophils in a four hour period in both premature and fullterm newborn infants. This result is in accordance with previous investigations by

KLEIN and HANSON (1950) and JAILER *et al.* (1951). The response of the eosinophils is admittedly lower in the newborn than in the adult, where usually a decrease of 50 per cent or more is obtained (THORN 1951), but apparently the adrenals of the newborn do react to ACTH. The question as to whether high doses of ACTH would cause a response more similar to that in adults cannot be answered from the data presented in this investigation. It is at present difficult to compare different preparations of ACTH, but it seems likely that the doses employed by KLEIN and HANSON (up to 12 mg) and by JAILER *et al.* (6 mg) are considerably higher than the doses used in this investigation. The decrease in eosinophils obtained by KLEIN and HANSON and by JAILER *et al.* seems, nevertheless, to be of about the same magnitude as that which we noted after administration of 1/3 or 2/3 mg per kilogram bodyweight. The fact that a comparison between the effects of these two doses does not show any significant difference seems also to indicate that the size of the doses of ACTH within these limits is of minor importance.

In older infants a better response to ACTH could be expected. From the data presented is seen that the same dose of ACTH as calculated on bodyweight (2/3 mg per kg) causes a greater decrease in the older infants (30—120 days old) than in newborn infants (0—7 days old). When, however, the possibly spontaneous variations in the number of eosinophils are taken into consideration, the difference between these two groups is not significant.

This result is at variance with that reported by KLEIN and HANSON. These authors found less response of the eosinophils in newborns under one week of age than in older infants. The explanation of these conflicting results may be found in the spontaneous change which KLEIN and HANSON did not consider.

The data presented in our investigation cannot give an answer to the question on the existence of a physiological transitory adrenal insufficiency in the newborn. If such a transitory insufficiency exists one would expect to find a much lower response to ACTH in the newborn than in older infants. Furthermore, the premature infant could be expected to show an increasing response to ACTH with increasing maturity, i. e. the degree of response

should be correlated to weight and to age. No such correlation could be demonstrated.

Epinephrine causes a decrease of the eosinophils presumably by releasing ACTH from the pituitary, but it has been shown by WHITE and SUTTON (1950) and by JAILER *et al.* (1951) that the response of the eosinophils is much less definite in premature newborns than in other infants. This fact could be taken as evidence either of a transitory adrenal insufficiency or of an immaturity in the pituitary-adrenal relationship. The results of the present investigation speaks in favour of a pituitary-adrenal immaturity as the cause of the lower response in the newborns.

In our investigation a somewhat lower response of the eosinophils to ACTH has been found in infants than is usually found in adults. This may be due to the size of the dose, although this explanation is not very likely. It would be of interest to test very high doses of ACTH in infants and compare the result with that obtained in adults.

The influence of cortisone on the number of eosinophils has been studied in connection with the treatment of rheumatoid arthritis and rheumatic fever, but the results seem to be conflicting (for ref. vide INGLE 1950). In the present investigation no influence of cortisone on the number of eosinophils in infants could be found in a four hour period.

Summary

1. The spontaneous change in the number of circulating eosinophils from 8 to 12 o'clock was investigated in full-term and premature infants 0—7 days old and in full-term infants 30—120 days old. This change is sometimes considerable. — 2. The change in the number of eosinophil leukocytes from 8 to 12 o'clock after the injection of small doses of ACTH ($^1/_3$ and $^2/_3$ mg per kilogram bodyweight) was investigated in the same groups of children. — 3. When the mean values of the change expressed in per cent of the number of eosinophils at 8 o'clock are considered, a decrease after administration of ACTH is found in all groups. A statistical analysis shows that no significant difference in the degree of this decrease exists between premature and full-term newborns (0—7 days old). Nor is it possible to find such a difference between full term, 0—7 days old infants and infants 30—120 days old. — 4. The degree of response in the premature could not be correlated to weight or age of the infant. —

5. Cortisone had no significant effect on the number of eosinophils, when tested in the same way as ACTH. — 6. The results are discussed and it is pointed out that, if it is assumed that the eosinophil response to ACTH is a test of adreno-cortical function, the data collected in this investigation are difficult to coordinate with the hypothesis, that there exists in the newborn a physiological transitory adrenal insufficiency.

Effets de l'ACTH sur l'éosinophilie sanguine chez les enfants.

1. Les variations spontanées du nombre des éosinophiles en circulation de 8 à 12 heures ont été étudiées chez des enfants à terme, et des prématurés âgés de 0 à 7 jours et également chez d'autres enfants nés à terme et âgés de 30 à 120 jours. Les variations sont parfois considérables. — 2. Les variations du nombre des leucocytes éosinophiles de 8 à 12 heures, après l'injection de faibles doses de A.C.T.H. ($^1/_3$ et $^2/_3$ de milligrammes par kilogramme de poids corporel) ont été étudiées dans les mêmes groupes d'enfants. — 3. Si l'on considère le pourcentage des valeurs moyennes des variations, du nombre des éosinophiles à 8 heures, on peut mettre en évidence qu'il existe une baisse après administration de l'A.C.T.H. dans tous les groupes. Une étude statistique montre qu'il n'y a pas de différence significative entre ces groupes: soit entre les prématurés et les nouveau-nés, nés à terme, âgés de 0 —7 jours. Il n'est pas possible non plus de mettre en évidence une différence entre les enfants nés à terme âgés de 0 à 7 jours et le groupe de ceux âgés de 30 à 120 jours. — 4. L'importance de la réponse chez les prématurés n'est pas en relation avec leur poids ou leur âge. — 5. La Cortisone n'a pas d'effet significatif sur l'éosinophilie sanguine lorsque l'on fait la recherche suivant le même mode que pour l'A.C.T.H. — 6. Les auteurs discutent les résultats obtenus et mettent en évidence que si l'on considère la réponse des éosinophiles à l'A.C.T.H. comme test de fonction cortico-surrénalienne, les chiffres recuillis au cours de ses travaux, sont difficiles à coordonner avec l'hypothèse d'une insuffisance surrénalienne physiologique transitoire chez les nouveau-nés.

Die Wirkung von ACTH auf die zirkulierenden Eosinophilen bei Säuglingen.

1. Die spontane Veränderung der Anzahl zirkulierender Eosinophiler von 8 bis 12 Uhr wurde bei vollausgetragenen und frühgeborenen Kindern im Alter von 0—7 Tagen sowie bei vollausgetragenen im Alter von 30—120 Tagen untersucht. Diese Veränderung ist bisweilen beträchtlich. — 2. In denselben Kindergruppen wurde die Veränderung der Anzahl eosinophiler Leukozyten von 8 bis 12 Uhr nach Injektion kleiner Dosen

von ACTH ($^1/_3$ und $^2/_3$ mg je Kilogramm Körpergewicht) untersucht. — 3. Betrachtet man die Mittelwerte der Veränderung, ausgedrückt in Prozent der Anzahl Eosinophiler um 8 Uhr, so findet man in allen Gruppen eine Abnahme nach Zufuhr von ACTH. Eine statistische Analyse ergibt, dass kein signifikativer Unterschied im Grade dieser Abnahme zwischen 0—7 Tage alten frühgeborenen und vollausgetragenen Kindern besteht. Ebensowenig ist ein solcher Unterschied zwischen vollausgetragenen Kindern im Alter von 0—7 Tagen und solchen im Alter von 30—120 Tagen feststellbar. — 4. Eine Korrelation zwischen dem Grade der Reaktion bei den Frühgeborenen und dem Gewicht oder Alter der Kinder konnte nicht konstatiert werden. — 5. Cortison hatte keine signifikative Wirkung auf die Anzahl der Eosinophilen, wenn es in derselben Weise geprüft wurde wie ACTH. — 6. Die Resultate werden diskutiert, und es wird darauf hingewiesen, dass, wenn man die Eosinophilenreaktion auf ACTH als ein Kriterium der adreno-corticalen Funktion ansieht, die bei dieser Untersuchung festgestellten Tatsachen schwer mit der Hypothese vereinbar sind, dass beim Neugeborenen eine physiologische transitorische adrenale Insuffizienz besteht.

El efecto ACTH sobre los eosinófilos circulantes en los niños.

1. Se han investigado las variaciones expontáneas del número de eosinófilos circulantes de 8 a 12 horas de la mañana en niños prematuros y en nacidos a término entre el 0—7 día de la vida y en nacidos a término de 30—120 días. Estas variaciones frecuentemente son considerables. 2. Las variaciones en el número de eosinófilos entre las 8 y 12 horas después de la inyección de pequeñas cantidades de ACTH ($^1/_3$ y $^2/_3$ mg por kilo de peso) fueron también investigadas en el mismo grupo de niños. 3. Cuando se consideran la significación de los valores de variación del número de eosinófilos en tantos por ciento a las 8 horas se encuentra en todos los grupos una disminución tras la administración de ACTH. El análisis estadístico muestra que no hay diferencias significativas en el grado de esta disminución entre los prematuros y nacidos a término en los 0—7 días de la vida, tampoco las hay entre los nacidos a término de 0—7 días y los niños de 30—120 días de edad. 4. El grado de respuesta en los prematuros no guarda correlación con el pseo o edad del niño. 5. La cortisona no muestra un efecto significativo sobre el número de eosinófilos cuando se experimenta en el mismo sentido que el ACTH. 6. Se discuten los resultados y se pone de manifiesto que si se considera la respuesta de los eosinófilos al ACTH como una prueba de función adreno-cortical los datos recogidos en estos experimentos son difíciles de coordinar con la hipótesis de que en el recién nacido haya una insuficiencia adrenal fisiológica transitoria.

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FROM QUEEN LOUISE CHILDREN'S HOSPITAL, COPENHAGEN.
CHIEF: PROFESSOR OLUF ANDERSEN, M. D.

Investigations into the Pyruvic Acid Concentration in Blood from Children with Convulsive Fits and Petit Mal and an Assessment of the Significance of Muscular Activity on Pyruvic Acid Estimations in Infants in General

by

CATO LODDING

During the past 15 years considerable interest has been attached to the study of pyruvic acid (p. a.), in particular to its concentration in blood under different physiological and pathological conditions. The most important results may be summarized as follows:

1. Phosphorylated aneurin (cocarboxylase) is required for the normal breakdown of carbohydrates (BANGA, OCHOA and PETERS, 1939), and the phosphorylation of aneurin takes place in all nucleated cells, and perhaps chiefly in the liver (GOODHART and SINCLAIR, 1939).

2. An increased p. a. concentration was demonstrated in blood from patients with B_1 avitaminosis (beri-beri) and a fall in the p.a. concentration in these patients during treatment with aneurin (LU, 1939). Values up to 2.72 mg per cent p. a. were found in beri-beri against 0.50 mg per cent in normal persons.

3. Raised p.a. values were demonstrated in blood from patients with diabetic acidosis and coma (MARKEES and MEYER, 1948). A mean value of 3.30 mg per cent was found in diabetic coma. In rabbits with alloxan-diabetic coma a fall was observed in the greatly increased p.a. values in the blood after addition of cocarboxylase, but not after addition of pure aneurin. The conclusion was drawn from these observations that the phosphorylation of aneurin is interfered with in diabetic coma. In humans with diabetic coma a clinical improvement has also allegedly been observed after addition of cocarboxylase in insulin resistant cases. Recently it was shown, however, that even in cases of pronounced diabetic acidosis no difference was found in the p.a. blood values between patients treated with and without cocarboxylase. (GILLILAND and MENCER,

1951). It is still an open question whether certain cases of insulin resistant diabetic coma can be saved by addition of cocarboxylase.

4. Raised p.a. values in the blood were demonstrated in severe liver diseases, such as decompensated cirrhosis and especially hepatic coma (MATUZIO and NESBITT, 1950). In hepatic coma p.a. values of 2.65 mg per cent were found in the blood. No fall in the p.a. concentration was seen to occur after addition of aneurin in these severe liver diseases, indicating impairment of the mormal function of the liver in the intermediary carbohydrate metabolism. Tolerance tests with p.a. may therefore be useful as tests of function in liver diseases.

5. Raised p.a. values were demonstrated in various conditions: non-diabetic acidosis, as for instance in cases of acetonaemic vomiting, infantile toxicosis, and conditions of starvation (PASSWEG, 1950), and also after X-ray damage, during pregnancy after the 20th week, and after anaesthesia (MARKERS, KÄSER, and LANZ, 1950).

6. A p.a. rise in the blood was demonstrated after intake of food, anoxia, and muscular activity. A particularly marked rise has been observed after muscular work causing more or less physical strain (JOHNSON and EDWARDS, 1937; FRIEDEMANN, HAUGEN, and KMIECIAK, 1945).

7. Raised p.a. values were found in prematurely born infants in proportion to that in infants born at term, a condition which persists even in the adult age (TALLQVIST, 1951).

Present Investigations

The object of the present investigation was to clarify whether children suffering from convulsive fits or petit mal have an abnormal p.a. concentration in the blood. These diseases might possibly be associated with a pathological carbohydrate metabolism, which again might manifest itself in the p.a. values in the blood. We know that p.a. influences the pH of the blood, and that a change in the acidity of the blood plays a part in epileptic fits.

The blood samples were not withdrawn immediately after the fits, as we would then expect to find raised values owing to the muscular activity and hypoxaemia, but under "basal" circumstances (fasting in bed in the morning) after a day without fits.

We examined 20 children between the ages of 2 months and 13 years suffering from convulsive fits or petit mal. The great majority of these cases had been included under the diagnosis of epilepsy (symptomatic or cryptogenic). However, owing to the uncertainty of this diagnosis, particularly in the cases of young

infants, we chose the designation of "convulsive fits and petit mal" instead of "epilepsy". The diagnoses were based on blood and C.S.F. tests, X-ray of the skull, electro-encephalography, and in some cases on air encephalography.

At the same time we examined as controls 25 children between the ages of 6 weeks and 14 years with unimportant diseases, but with no tendency to convulsive fits or petit mal.

Method

The method described by BUEDING and WORTIS was employed: The blood is stabilized with iodo acetic acid and sodium fluoride, precipitated with trichloracetic acid, dinitrophenyl hydrazine added and then extracted first with aethylacetate and afterwards with sodium carbonate. The color intensity is estimated colorimetrically after addition of sodium hydroxide. In the present cases this was done by means of a Pulfrich's photometer. For blank analysis, a solution freshly prepared each time but using distilled water instead of blood, was made. Our only deviation from this method was that we used small test tubes (volume about 12 ml) with rubber stoppers for the extraction. The extraction was then performed by slow movements of the tubes, about 2 minutes each time.

BUEDING and WORTIS found values ranging between 0.77 and 1.16 mg per cent normal humans from 8 to 48 years of age, and regarded values over 1.30 mg per cent as pathological.

Results

In the control group values ranging from 0.83 to 2.07 mg per cent were found, mean value 1.30 mg per cent. In the cases with convulsive fits and petit mal values from 0.86 to 2.08 mg per cent were found, mean value 1.43 mg per cent.

Discussion

The mean value for p.a. concentration in blood from children with convulsive fits and petit mal thus differed only little from that in the control group (1.43 and 1.30 mg per cent respectively). Both mean values were, however, rather high, and both groups showed a strikingly great standard deviation of the values. Many values over 1.30 mg per cent were found, which according to BUEDING and WORTIS should be the upper normal limit for the

p.a. concentration in blood. This figure of 1.30 mg per cent was, however, found on the basis of individuals over 8 years of age.

TALLQVIST studied the p. a. values in different age groups up to the age of 40 and found a falling p. a. concentration in blood with increasing age. In his series of cases, however, the mean values for p.a. remained at approximately the same level throughout childhood, except for slightly higher values during the first week of life.

When estimating the p. a. concentration in blood from *infants under 5 years of age* we must take into consideration the fact that the majority do not remain quiet during the blood sampling. Some of the children examined here were sweating, hot, and out of breath. There was, in all cases, a rather considerable muscular tension, which means that the muscles were at work during the sampling. The patient with the highest p. a. concentration on the blood displayed the greatest muscular activity of all during the blood sampling.

The following experiments were made to investigate the rise in the p. a. concentration in blood after bodily exertion of short duration. Six patients (5 from the control group and 1 from the convulsive-petit mal group) between the ages of 7 and 13 had their blood examined for p. a. while at rest. Then the first patient performed very light muscular work (rose and sat down 10 times within 30 seconds), and the next performed increasing muscular work. Thus we could estimate the p. a. concentration after different degrees of physical strain. Fresh blood samples were withdrawn immediately after the conclusion of the muscular work. The results appear in Table 1.

The experiments showed that exertion causes a considerable rise in the p. a. concentration in blood even in cases with no signs of physical strain (hot skin, sweating, breathlessness). This result is in agreement with those of the investigations already mentioned into the p. a. rise in the blood of adults after exertion.

If we divide the present series of cases into two groups with children over and under 5 years of age (and to have the children under 5 who could not be kept at rest during the sampling kept in a separate group) it appears that the mean values for both

Table 1.

The pyruvic acid (p.a.) rise in the blood of children after increasing degrees of short muscular exertion.

No	P. a. at rest mg per cent	Muscular work	Degree of strain	P. a. after strain mg per cent	P. a. rise per cent
Control group no 18	0.83	Rose and sat down 10 times within 30 sec.	Not breathles, not hot	1.03	24
Control group no 17	1.03	Rose and sat down 20 times within 60 sec.	Not breathless, not hot	1.33	29
Control group no 21	0.91	Ran 48 steps up and down within 30 sec.	Slightly breathless, not hot	1.45	58
Control group no 14	1.15	Ran 48 steps up and down 4 times within $2^1/_2$ min.	Breathtless, slightly hot and sweating	2.04	77
Control group no 23	1.39	Ran 48 steps up and down 7 times within 6 min.	Highly breathless, hot and sweating	2.95	113
Convulsive-petit mal group no 15	1.36	Ran 48 steps up and down 10 times within $8^1/_2$ min.	Highly breathless, very hot and sweating	3.84	183

Table 2.

Mean pyruvic acid (p.a.) valaues in blood from children over and under 5 years of age, in the convulsive-petit mal group and the controlgroup.

	Total mean value mg per cent	Mean value over 5 years mg per cent	Mean value under 5 years mg per cent
Convulsive-petit mal group	1.43	1.20	1.54
Control group	1.30	1.14	1.54

the convulsive-petit mal group and the control group were at a normal level in children over 5, whereas in both groups under 5 they were much above the normal limit.

Fig. 1 shows the mean p.a. values in blood in relation to age.

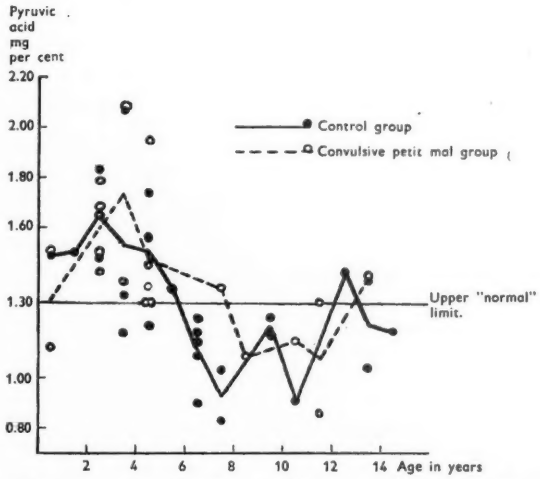

Fig. 1. Mean pyruvic acid values in blood in the different age groups.

Two of the infants of this series were prematurely born, i.e., they had had a birth weight under 2500 g. In both cases the p. a. values were sligthly below the average for the age (both 1.30 mg per cent.)

Summary

The pyruvic acid concentration was estimated in blood from 20 children between the ages of 2 months and 13 years suffering from convulsive fits or petit mal. 25 patients between the ages of 6 weeks and 14 years with no tendency to convulsive fits or petit mal served as controls. A mean value of 1.43 mg per cent was found in the convulsive-petit mal group (extremes 0.86 and 2.08 mg per cent), while in the control group the mean value was 1.30 mg per cent (extremes 0.83 and 2.07).

In the patients over 5 years of age, who generally kept quiet during the sampling, normal mean values were found both in the convulsive-petit mal group and the control group. Those under 5 years of age, who never were at rest during the sampling, presented abnormally high mean values in both groups. The high pyruvic acid values are probably attributable to the great muscular activity displayed by these infants during the venepuncture. Experiments were made which showed that in children even light muscular work produces a rather considerable rise in the pyruvic acid concentration in blood. The conclusion is drawn that no

significant difference is found between children with convulsive fits or petit mal and a control series with regard to the pyruvic acid concentration in blood.

Recherches sur la concentration d'acide pyruvique dans le sang des enfants avec crises convulsives et petit mal, — et evaluation de l'influence de l'activité musculaire sur les taux d'acide pyruvique chez l'enfant en général.

La concentration d'acide pyruvique a été dosée dans le sang de 20 enfants entre les âges de 2 mois à 13 ans, atteints de crises convulsives ou de petit mal. 25 malades entre les âges de 6 semaines à 14 ans, sans tendance aux crises convulsives ou petit mal, servent de contrôle. Une valeur moyenne de 1,43 mg % a été trouvée dans le groupe des malades avec convulsions ou petit mal (valeurs extrêmes, 0,86 et 2,08 mg %), tandis que dans le groupe de contrôle, la valeur moyenne était de 1,30 mg % (extrêmes 0,83 et 2 07). Chez les malades au-dessus de 5 ans, qui généralement restent calmes pendant la prise de sang, des valeurs moyennes normales ont été trouvées dans les deux groupes, avec crises convulsives ou petit mal et le groupe de contrôle. Les enfants au-dessous de 5 ans qui n'ont jamais été au repos durant la prise de sang, présentent des valeurs moyennes anormalement élevées dans les deux groupes. Les valeurs élevées d'acide pyruvique sont probablement dûes à la grande activité musculaire déployée chez ces enfants, durant la ponction veineuse. Des expériences ont été faites qui montrent que, chez l'enfant, même un léger travail musculaire produit une augmentation assez considérable de la concentration de l'acide pyruvique dans le sang. On en conclut qu'il n'y a pas de différence significative, entre les enfants avec convulsions ou petit mal et la série de contrôle, en ce qui concerne la concentration d'acide pyruvique dans la sang,

Untersuchungen über die Konzentration von Brenztraubensäure im Blute von Kindern mit Krampfanfällen und Petit mal, sowie allgemeine Beurteilung der Bedeutung von Muskeltätigkeit in Bezug auf Brenztraubensäurebestimmungen bei Kleinkindern.

Die Konzentration von Brenztraubensäure im Blute wurde von 20 an Krampfanfällen oder Petit mal leidenden Kinder im Alter zwischen 2 Monaten und 13 Jahren bestimmt. Kontrolluntersuchungen wurden an 25 Patienten im Alter zwischen 6 Wochen und 14 Jahren ohne Neigung zu Krampfanfällen oder Petit mal minor durchgeführt. In der ersten Gruppe wurden durchschnittliche Werte von 1,43 mg % (Extreme 0,86 und 2,08 mg %) ermittelt, während in der Kontrollgruppe die Durchschnitts-

werte 1,30 mg.% (Extreme 0,83 und 2,07) betrugen. Bei Patienten über 5 Jahre, welche sich im allgemeinen während der Probe ruhig verhielten, wurden sowohl in der Krampfanfalls- und Petit mal-Gruppe als auch in der Kontrollgruppe normale Durchschnittswerte ermittelt. Jene Kinder unter 5 Jahren, welche sich niemals während der Untersuchung ruhig verhielten, wiesen in beiden Gruppen abnormal hohe Durchschnittswerte auf. Der hohe Gehalt an Brenztraubensäure kann wahrscheinlich der heftigen Muskeltätigkeit dieser Kinder während der Venenpunktion zugeschrieben werden. Es wurden Versuche durchgeführt, welche bewiesen, dass bei Kindern sogar leichte Muskelarbeit eine ziemlich beträchtliche Erhöhung der Konzentration von Brenztraubensäure im Blute bewirkte. Es wird daraus geschlossen, dass es in Bezug auf die Konzentration von Brenztraubensäure im Blute zwischen Kindern mit krampfartigen Anfällen oder Epilepsia minor und einer Kontrollserie keinen bedeutungsvollen Unterschied gibt.

Investigaciones sobre la concentración sanguínea en ácido pirúvico en niños con crisis convulsivas y pequeño mal y estudio sobre la significación de la actividad muscular en relación con la determinación de la piruvinemia en niños en genreal.

En 20 niños de edad comprendida entre 2 meses y 13 años afectos de crisis convulsivas o de pequeño mal se han hecho determinaciones de la concentración en sangre de ácido pirúvico. Como control se han usado 25 niños de edad comprendidos entre 6 semanas y 14 años sin tendencia convulsiva o pequeño mal. Se encontraron en el grupo convulsiones-pequeño mal unos valores medios de 1,43 mg. % (valores extremos 0,86 y 2,08 mg %) mientras que en el grupo de control los valores medios fueron de 1,30 mg % (extremos 0,83 y 2,07). En los niños por encima de 5 años de edad los cuales generalmente están quietos durante la extracción de sangre se encontraron valores medios normales en ambos grupos, mientras que los niños por debajo de 5 años los cuales durante la toma de sangre nunca están quietos presentaron tanto en el grupo convulsivo-pequeño mal como en el grupo de control valores medios anormalmente elevados. Estos valores de piruvinemia altos deben atribuirse probablemente a la elevada actividad muscular desarrollada por estos niños mientras se hace la puntura venosa. Se han realizado experimentos para demostrar que en los niños siempre un ligero trabajo muscular produce una notable modificación de la concentración del ácido pirúvico en sangre. Se dá la conclusión que no se han encontrado diferencias significativas entre niños afectos de crisis convulsivas o pequeño mal y otras series de control en lo que se refiere a sus cifras de ácido pirúvico en sangre.

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The Effect of Universal Carbon-Arc Light Therapy on the Development of Immunity

by

SV. HEINILD, P. Q. EDWARDS, K.-E. FOGHT-NIELSEN, K. G. HANSEN, K. MAGNUS and I. SCHEIBEL

Introduction

Today, more than 50 years after FINSEN'S fundamental investigations concerning the effect of light on the living organism (1), a strange contrast still exists between the faith of the public in the beneficial effect of light treatment and the inability of science to determine the source of this postulated beneficial effect. Mention of light treatment here and in the following refers exclusively to artificial universal irradiation of the human body with ultra-violet rays — the so-called chemically effective part of the spectrum, i. e., the wave-length 3900—1000 Ång. Today it must be acknowledged, as stated so aptly at the last Congress for treatment with ultra-violet rays, held at Hanau in January 1950, that: "die Ultravioletttbehandlung in den Krankenhäusern und Kliniken auf das Niveau der Schwesternbehandlung herabgesunken ist" (2).

In a work published in 1944 (3), one of the writers (S. H.) tried to approach the problem from one definite angle, viz., the effect on blood. He found that no effect could be demonstrated with regard to haemoglobin per cent, sedimentation rate, and the

white blood count. As a consequence of these findings, a further series of experiments are in progress at the Paediatric Out-Patient Department of the Finsen Institute, which functions as a diagnostic centre for patients referred to the Light Therapy Clinic there. These studies deal with the possible influence of carbon-arc light therapy on the formation of antibodies and the development of immunity, and on the course of diseases of the upper respiratory tract in children. The first of these investigations, which are reported in this paper, have been carried out, in collaboration, by the Serum Department of Statens Seruminstitut, the World Health Organization Tuberculosis Research Office, and the Finsen Institute.

A great number of investigations have been made previously concerning the biological effect of universal light therapy. The results of these are by no means in agreement. Many might be repeated today with improved technique and, perhaps, better understanding of the reactions of the organism than existed during the first 25 years of this century.

These earlier studies fall into the following well-defined groups: The effect of light on (i) skin, (ii) metabolism, (iii) respiratory system, (iv) blood and circulatory system, (v) growth, (vi) neuromuscular system, (vii) heat production and body temperature, (viii) mechanism of response to infection.

In addition there are reports of extensive investigations concerning the source, and some — but unfortunately only few — dealing with ways of measuring the effects of light. A critical evaluation of this comprehensive literature is outside the scope of the present paper; for a review of the literature reference should be made to "*Lehrbuch der Strahlentherapie*" (4) and MAYER. (5)

Present Investigations

Patient material and light treatment

The present investigations have been carried out among children, 4—15 years of age, referred to the Light Therapy Clinic at the Finsen Institute, Copenhagen, and the Coast Hospital at Refsnæs, in the period November—March, 1949—1950 and 1950—1951 (in order to minimize exposure to sunlight).

Practically all the children were diagnosed as having various degrees of upper respiratory tract infections, or behaviour disturbances; many of the children had a combination of both. The Refsnæs patients also include a number of asthma cases. None of the children were febrile or showed any evidence of active tuberculosis during the investigation periods.

The material has been selected from among the Finsen Clinic patients, who, for other purposes, are divided at random into two equal-sized groups. One group is given universal carbon-arc light treatment, in accordance with the following schedule:

1st day:	4	minutes
3rd day:	6	»
5th day:	10	»
7th day:	14	»
9th day:	18	»
11th day:	24	»
13th day:	30	»

and thereafter 30-minute periods every other day for a total of 20 to 30 treatments in each series. The other group is used as control material, and during the whole observation period these children are treated according to the same schedule with irradiation from a Sollux-lamp consisting of very slight emission of ultra-violet A (about 0.1 per cent of the total irradiation emission) but very strong emission of infra-red. At the Refsnæs hospital, the same schedule for carbon-arc treatment was followed, but the control group was not treated in any way.

I

The Effect of Ultra-Violet Light on the Formation of Antitoxin

(I. SCHEIBEL and K.-E. FOGHT-NIELSEN)

The aim of this section is to examine whether the production of antibodies (antitoxin) is affected by universal light treatment administered before and after immunization. Since the introduction of light therapy, this subject has occupied several investigators on the belief that light treatment has a resistance-increasing and restorative effect on the organism. The results of these former investigations have been divergent, having shown a pronounced effect, no effect, and an inhibitory effect.

The conditions for these experiments have varied considerably, both as regards antigen and light treatment. Generally, particulate antigens such as various bacterial emulsions have been used, and only infrequently have dissolved antigens been employed (albumin, bacterial toxins). Often no details are given regarding the source of light, dose or duration of irradiation, and sometimes adequate control material is lacking. This presumably explains to some extent the divergent results obtained.

Brief mention will be made here of some of the works known to the writers.

POTTHOFF & HEUER (6) found slight activation of agglutinin production in guinea-pigs after typhus vaccination, this being most pronounced in animals which had been subjected to irradiation on depilated skin. These authors found, in rabbits and guinea-pigs which were already immune, a pronounced increase in agglutinin content after the first irradiation, while continued irradiation caused disappearance of antibodies more rapidly than in the control animals.

Comprehensive studies made by BESSEMANS & SELDESLACHTS (7) showed that irradiation with a mercury lamp increased the maximal titre of typhus agglutinin in vaccinated shaved rabbits, when irradiation was commenced two to four days before the injection of prophylactic, but not if it was started at the same time or after the injection. Irradiation before or at the same time as injection of prophylactic caused more rapid agglutinin production.

POLI & ALEXANDRE (8) obtained slightly increased production of antibodies to typhus bacteria and albumin in rabbits after simultaneous ultra-violet irradiation (quartz lamps) and injection of quinine salt, but not in animals which were treated with either irradiation or quinine only.

It is possible that statistical analysis of the figures, taking the often quite limited number of animals used in the various investigations into consideration, might have revealed in certain cases that increases of the order of magnitude found were not sufficient basis for concluding a possible cause of light treatment.

HARTLEY (9) found no influence on typhus agglutinin production after irradiation of non-depilated rabbits with mercury or carbon-arc lamps.

KONRICH (10) found that ultra-violet rays did not affect agglutinin production in rabbits (immunized with Eberthella) and KAMEKURA (11) could show no effect on the agglutinin curve in rabbits with natural Eberthella antibodies.

HARDY & CHAPMAN (12) concluded from their experiments that even

prolonged irradiation with ultra-violet light has no effect on the complement titre in rabbits during immunization with pneumococci.

As far as is known to the writers, only a very few studies have been directly aimed at measurement of antibodies in humans.

HANSEN (13) found "favourable" effect on the antibody curve after typhus immunization in 30 patients with lupus and bone tuberculosis, but no mention is made of any control material.

Using a very large material composed mostly of children WILDFÜHR (14) examined the natural diphtheria antitoxin level with and without light treatment, the production of antitoxin after immunization of persons not naturally immune, and the speed at which antitoxin production commences after "recall" injection in naturally immune and previously artificially immunized persons.

The studies were carried out in the winter months and the light treatment was administered in the form of universal mercury/quartz light. He reported a pronounced accelerating effect in all groups; about 58 per cent of 1109 non-irradiated children showed $< 1/20$ A. U. natural antitoxin, as against about 23 per cent in the irradiated group (399 children). After two injections of an adsorbed diphtheria prophylactic, 66 per cent who received no light treatment (604 children) had produced $> 1/20$ A. U. as against 86 per cent of the 360 light-treated children. In naturally immune and previously-immunized children having between 1/20—1/10 A. U./ml, a recall injection is reported to cause, *within 15 hours*, a 5—10 fold increase in 15 per cent of 354 non-irradiated subjects in contrast to 55 per cent among the 200 light-treated. This latter observation is surprising, since several workers who have examined this question very thoroughly have not observed production of antitoxin after recall injection until, at the earliest, on the second or third day, and then only as a slight increase, while the explosive production of antitoxin is not observed before the fourth to sixth day. Wildführ makes no comment on this new observation.

Present Investigations

As an index of the production of antibodies, we chose tetanus antitoxin because, at the time the work was carried out, active tetanus immunization was so little used in Denmark that it was not difficult to find non-immunized children suitable for observation of both primary and secondary response, and because natural immunity against tetanus as the result of latent infection is not known. (To our knowledge, only one positive finding has been reported, viz., TENBROECK & BAURER (15), while other workers,

i. e., RAMSON & ZOELLER (16), BERGEY & ETRIS (17), ERICSSON *et al.* (18), SCHEIBEL & BOJLEN (19), have not been able to confirm this.) In this way the complication of naturally-acquired immunity could be avoided in the interpretation of artificial immunization, and it could be assumed in advance that all children would be suitable for participation in the study.

At the commencement of the investigation blood sedimentation tests were made on all the children by the Westergren method. The sedimentation rates varied between 3 and 25 mm, with the single exception of 89 mm. Distribution was uniform in the various groups, and no relation could be found between the initial blood sedimentation rate and the first or second antitoxin response.

The investigation was planned as follows:

4 weeks' light treatment (see page 417)
Blood test for antitoxin determination I — tetanus immunization I
4 weeks' light treatment (see page 417)
Blood test for antitoxin determination II — tetanus immunization II
2 weeks' light treatment (see page 417)
Blood test for antitoxin determination III

The tetanus prophylactic used was a toxoid purified by ultrafiltration, adsorbed to $Al(OH)_3$ (SCHEIBEL) (20). The injection dose of 1 ml contained about 12.5 units tetanus toxoid and $Al(OH)_3$-gel corresponding to 1 mg aluminium. The injections were given subcutaneously in the supraspinal region.

The titrations were made subcutaneously on mice by the IPSEN method for the determination of small quantities of tetanus toxin (21). All the sera were titrated individually. The geometric mean of the titres for each group and the frequency of children who, after the first injection, had definite measurable antitoxin production, i. e., > 0.001 A. U., and those who, after the second injection, had $\geqq 0.01$ A. U./ml (which is normally regarded as the minimum for protection), are shown on Tables 1 and 2.

The means after one injection (before the second injection) are lower in both light-treated groups. However, these means must only be taken as mere approximations, because the majority of the children did not react with measurable antitoxin production after the first injection, in accordance with previous experience (SCHEIBEL & BOJLEN) (19), and because measurement at these low levels is necessarily inaccurate. In addition, the standard devia-

Table 1

The effect of universal carbon-arc irradiation on the production of tetanus antitoxin after the first and second injection of tetanus prophylactic in children at the Finsen Institute.

	Number of children	Titre before first injection	Titre before second injection			Titre 2—4 weeks after second injection		
		Geom. mean A. U./ml	Geom. mean A. U./ml	≧ 0.001 A. U./ml		Geom. mean[1] A. U./ml	≧ 0.01 A. U./ml	
				Number	Per cent		Number	Per cent
Carbon-arc treated	13	< 0.00005	0.00027	4	33[2]	0.089	12	92[2]
Controls	9	< 0.00005	0.0006	5	57	0.11	9	100

[1] Standard deviations of 0.61 and 0.45, respectively.

[2] One child not tested.

Table 2

The effect of universal carbon-arc irradiation on the production of tetanus antitoxin after the first and second injection of tetanus prophylactic in children at the Coast Hospital, Refsnæs.

	Number of children	Titre before first injection	Titre before second injection			Titre 2—4 weeks after second injection		
		Geom. mean A. U./ml	Geom. mean A. U./ml	≧ 0.001 A. U./ml		Geom. mean[1] A. U./ml	≧ 0.01 A. U./ml	
				Number	Per cent		Number	Per cent
Carbon-arc treated	12	< 0.00005	0.0004	3	25	0.14	12	100
Controls	12	< 0.00005	0.0005	4	33	0.08	11	92

[1] Standard deviation of 0.53 and 0.57, respectively.

tion is very great (> 1) within the individual groups and the mean differences observed are thus far from significant. The percentage of children who produced > 0.001 A.U. after the first injection is likewise lower in both of the carbon-arc light-treated groups, but statistical evaluation shows that these variations are not significant either within the same institution or between the two different institutions. For instance, by comparing the two groups showing the greatest divergence, viz., the carbon-arc light-treated group at Refsnæs (25 per cent) and the control group at the Finsen Institute (57 per cent), a P of 30 per cent is found.

After the second injection, the light-treated group at the Finsen Institute shows a 20 per cent lower mean titre than the control group, whereas the opposite is the case at Refsnæs, where the light-treated group has an average titre about 75 per cent higher than that of the control group.

Statistical evaluation shows that both the apparently inhibitory effect in the group at the Finsen Institute and the accelerating effect in the Refsnæs material are very probably only random variations around the true mean value; with the standard deviation in question, to secure significant difference, the one mean should be at least three times the other.

The percentage of children who produced more than 0.01 A.U./ml after the second injection is, generally speaking, uniform in all four groups, since only two of the 46 children did not attain the protection limit; one of these was in a light-treated group (Finsen) and the other in a control group (Refsnæs).

Table 3 shows the results with a few other children at the Finsen Institute who were immunized but who did not have the final blood test taken, which means that only the antitoxin production after the first injection could be followed up. Otherwise the conditions for examination of these children were as described above.

Again in the case of these children, light treatment has not led to increased antitoxin production. The figures for preponderance in the control group, both as regards mean titre and frequency of children producing antitoxin, lie within the limits of error for the investigation.

Table 3

The effect of universal carbon-arc irradiation on the production of tetanus antitoxin after one injection of tetanus prophylactic in children at the Finsen Institute.

	Number of children	Titre before first injection	Titre after the first injection		
		Geom. mean A. U./ml	Geom. mean A. U./ml	≥ 0.001 A. U./ml	
				Number	Per cent
Carbon-arc treated ...	5	<0.00005	0.00027	1	20
Controls	9	<0.00005	0.00055	4	44

Discussion

On the basis of our experiments, it must be concluded that universal carbon-arc light treatment does not seem to have any particular influence on the production of antitoxin, either at the first contact of an organism with the antigen, or in an organism which is already activated.

This is an obvious contrast with the most recent results published in this field (WILDFÜHR, 1950 (14)), where the two sets of investigations can be considered to have been conducted along roughly the same lines. There is no reason for assuming that the mechanism which is responsible for production of diphtheria antitoxin is very different from that which produces tetanus antitoxin; furthermore, both diphtheria and tetanus antigens were administered in the same form, i. e., as an $Al(OH)_3$ adsorbate. The investigations are not, of course, directly comparable statistically, because the units of diphtheria and tetanus antitoxins are not synonymous, and because the titrations in WILDFÜHR's studies are not carried out beyond a chance limit and, therefore, give no information concerning the distribution or the placing of that section of the distribution which underlies the calculated relative frequencies. However, these factors do not seem to us to be a

satisfactory explanation of the divergent results of the investigations.

Then there is the light treatment itself. Mercury/quartz light, which WILDFÜHR used, has a discontinuous spectrum consisting of very intensive spectral-lines all over the ultra-violet (short-wave as well as long-wave), including the spectral bands which are considered active in erythema, pigment or D-vitamin formation. The spectrum of carbon-arc light used in our investigations, on the other hand, is continuous, with a very considerable intensity in violet and the long-wave part of the ultra-violet band, whereas the intensity in the short-wave ultra-violet band (below 300 μ), including the vitamin-forming spectral band, is rather low.

At the present time it is not known whether such qualitative and quantitative differences as those just mentioned may have a significant effect on the antitoxin-producing mechanism. Further experiments directed toward a comparison of the two different sources of light are needed. It is obvious from these investigations as well as from other studies reported in the literature that up to the present time too little attention has been paid to accurate dosimetry and that this important factor should not be overlooked in further research in this field.

II

The Effect of Carbon-Arc Therapy on Tuberculin Sensitivity and BCG Vaccination

(P. Q. EDWARDS and K. MAGNUS)

Although the relationship between allergy and immunity in tuberculosis is still uncertain, sensitivity to tuberculin as measured by the tuberculin test is widely used in practical work as an index of immunity. In the absence of clinical disease, reactors to tuberculin are usually assumed to possess some degree of immunity and the success or failure of BCG vaccination is expressed in terms of post-vaccination tuberculin allergy. Moreover, although there is little supporting evidence, the view is rather widely held that the

degree of immunity produced by BCG quantitatively corresponds to the size of the induced tuberculin reaction.

Several earlier studies concerning the effect of sunlight or artificial heliotherapy on the tuberculin reaction have reported a reduction in sensitivity in most of the subjects. As early as 1920 MAYER (22) pointed out that tuberculin skin tests on areas exposed to ultra-violet irradiation were negative whereas control tests on areas not irradiated remained positive. In confirming this observation TURIN (23) expressed the opinion that "a good state of immunity, as has already been shown to be acquired by ultra-violet irradiation, also creates a diminished state of allergy."

Conflicting reports are sufficiently numerous, however, to leave the question unsettled. DE BONIS (24), for example, reported from a study of more than one thousand children that, although the reactions appeared to be weakened after heliotherapy in a good many cases, in about 10 per cent of the children the reaction became more intense and in 6 per cent a reaction appeared even though it had been absent before heliotherapy. CORTELLA (25) observed that in almost one-quarter of his subjects treated with ultra-violet rays there was an accentuation of the tuberculin reaction while in a little over 60 per cent a depression of sensitivity was noted, whereas TALON-CHAUVEAU *et al.* (26) found reactions considered negative in only 28 of 52 subjects with positive reactions before irradiation.

In the laboratory, HELMS (27) was not able to demonstrate any difference in the size of tuberculin reactions six weeks after infection with virulent bovine bacilli between a group of guinea-pigs treated with artificial heliotherapy and the untreated controls.

Since tuberculin testing is so widely used, particularly in BCG vaccination programs, it is of considerable practical importance to know more of the quantitative relationship between the tuberculin reaction and exposure to light. The present paper reports the results of a small but carefully controlled study designed to obtain information on the effect of generalized over-all exposure of the bodies of children to a routinely used course of carbon-arc light therapy. Specifically, three questions were asked: First, is the size of induration of the tuberculin reaction in children having reactions regarded as positive, changed by a 5-weeks' course of such light treatment? Second, is the development of tuberculin allergy influenced by light therapy given during a 6-weeks period immediately following BCG vaccination? Third, in the same vacci-

nated children as above, is the size of induration of the vaccination lesion influenced by the artificial heliotherapy?

The present study was carried out between the last week of January and the middle of March 1951, a period in which eighty hours of sunlight were recorded in Refsnæs and forty-two hours in Copenhagen to which the children might have been exposed had they been out-of doors whenever the sun shone. Medical supervision of the light therapy and facilities for the study were provided by the Finsen Institute; the Tuberculosis Research Office of the World Health Organization was responsible for study plans, performance of testing and vaccination, and analysis of results.

Effect on tuberculin sensitivity

For the purpose of studying the effect of carbon-arc light on tuberculin sensitivity in tuberculin positive children, two groups of children four to fifteen years old attending the ambulatory light clinic at the Finsen Institute were given a tuberculin test, and five weeks later the test was repeated. In the interval between the two tests, one group received the course of carbon-arc therapy routinely in use at the clinic. The other group was given similar exposure to the control apparatus. Only those whose initial reaction was at least 6 mm of induration were included in the study group which, because of losses, consisted of twenty-seven children who finished the course of therapy with completed tests. Allocation to treated or control group was made by alternation of the children.

The technical procedures were performed by specially trained nurses who did not know the purpose of the study or which children were being exposed to light. One nurse gave all the tuberculin tests by intradermal injection of 10 T. U.[1] (0.0002 mg) of PPD dilution (0.1 cc) in the left dorsal forearm. Through a misunderstanding, retesting was with 5 T. U.[1] (0.0001 mg) although, fortunately, this error has no bearing on the results of the study. The reactions were read on the third day by a nurse who dictated her measurements of the transverse diameter of erythema and induration to a secretary.

The measurements of induration of the tuberculin reactions in the two groups of children are shown in Table 4. Before starting treatment there was no difference between the two groups in the

[1] PPD, batch RT XIX, XX, XXI, State Serum Institute, Copenhagen.

Table 4

Mantoux reactions by size of induration before and after five weeks of exposure to carbon-arc light or control apparatus among twenty-seven children at the Finsen Institute, Copenhagen, 1951.

Child No.	Light-treated			Child No.	Controls		
	Size of induration in mm				Size of induration in mm		
	1st test (Mx. 10 T. U.)	2nd test (Mx. 5 T. U.)	1st–2nd test		1st test (Mx. 10 T. U.)	2nd test (Mx. 5 T. U.)	1st–2nd test
1	8	13	− 5	1	6	11	− 5
2	9	5	+ 4	2	7	7	0
3	11	10	+ 1	3	8	9	− 1
4	13	13	0	4	8	5	+ 3
5	15	13	+ 2	5	11	8	+ 3
6	15	12	+ 3	6	13	12	+ 1
7	16	14	+ 2	7	13	13	0
8	16	6	+10	8	16	19	− 3
9	16	11	+ 5	9	16	13	+ 3
10	20	11	+ 9	10	17	13	+ 4
11	21	15	+ 6	11	18	11	+ 7
				12	18	10	+ 8
				13	19	15	+ 4
				14	19	8	+11
				15	20	10	+10
				16	22	14	+ 8
Arithmetic mean	14.54	11.18	3.36	Arithmetic mean	14.44	11.13	3.31

mean size of induration — 14.5 mm for those allocated to the light group and 14.4 mm for the controls. Retesting showed a mean reaction size of 11.2 mm for the light group and 11.1 mm for the controls, indicating that the routine carbon-arc therapy had no effect on the sizes of the tuberculin reactions. Reactions for both groups are significantly larger on the first test, however, because 10 T. U. was used for the first test and only 5 T. U. for the second.

Table 5

Distribution by size of induration of vaccination lesion of light-treated (L) and controls (C) read at weekly intervals among twenty-seven children at the Refsnæs Coast Hospital, Denmark, 1951.

Induration (mm)	Interval between vaccination and reading (days)													
	3		12		17		24		32		38		44	
	L	C	L	C	L	C	L	C	L	C	L	C	L	C
0	—	—	—	—	—	—	—	—	—	—	—	—	—	—
1	—	—	—	—	—	—	—	—	—	—	—	—	—	—
2	—	—	—	—	—	—	—	—	—	—	—	—	—	—
3	6	3	—	—	—	—	—	—	—	—	—	—	—	—
4	5	6	4	2	1	1	—	—	—	—	—	—	—	—
5	1	3	4	7	3	—	—	1	—	—	—	—	—	—
6	1	1	4	2	3	5	—	1	—	—	—	—	—	1
7	—	—	—	2	3	4	2	3	—	—	—	—	—	—
8	—	—	—	1	—	2	2	2	—	2	—	—	1	—
9	—	—	—	—	1	—	3	1	1	1	—	2	1	1
10	—	1	—	—	—	1	2	—	1	—	2	2	4	6
11	—	—	—	—	—	—	1	—	—	2	1	2	1	—
12	—	—	1	—	—	1	—	1	3	1	3	1	2	1
13	—	—	—	—	—	—	—	—	3	1	—	—	1	1
14	—	—	—	—	—	—	1	1	1	—	1	—	1	—
15	—	—	—	—	—	—	—	1	1	2	3	—	1	—
16	—	—	—	—	1	—	—	1	1	2	1	1	1	1
17	—	—	—	—	1	—	—	1	1	2	1	1	—	—
18	—	—	—	—	—	—	—	—	—	—	—	1	—	—
19	—	—	—	—	—	—	—	1	—	—	—	—	—	—
20	—	—	—	—	—	—	1	—	—	—	1	2	—	—
21	—	—	—	—	—	—	—	—	1	—	—	—	—	—
22	—	—	—	—	—	—	1	—	—	—	—	—	—	—
23	—	—	—	—	—	—	—	—	—	—	—	—	—	—
24	—	—	—	—	—	—	—	—	—	—	—	—	—	1
25	—	—	—	—	—	—	—	—	—	1	—	2	—	1
Total	13	14	13	14	13	14	13	14	13	14	13	14	13	14
Arithmetic mean	3.77	4.57	5.54	5.50	7.69	7.14	11.08	10.21	13.62	13.79	13.77	15.21	11.54	13.07

Effect on BCG vaccination lesions and post-vaccination sensitivity

In mid-January graduated doses of light therapy were started at the Refsnæs Coast Hospital on twenty-seven non-vaccinated children ranging in age from two to eleven years. Tuberculin tests two weeks later were all read as showing an induration of less than 6 mm, so each child was given an intradermal injection of 0.1 cc of BCG (batch 929, State Serum Institute, Copenhagen). The children were then divided by a random method into two groups, one to continue light therapy with maximal dosage given within one hour of vaccination and daily for seven days, three times weekly thereafter, and the other to serve as controls with no further light treatment. Thus, at the time of vaccination, both groups were comparable with respect to obviously relevant factors.

Vaccination lesions were observed at weekly intervals by a nurse who

Table 6

Distribution by size of induration of Mantoux 5 TU reactions six weeks after BCG vaccination of light-treated and controls among twenty-seven children at the Refsnæs Coast Hospital, Denmark, 1951.

Size of induration (mm)	Light-treated	Controls
0	—	—
1	—	—
2	—	—
3	—	—
4	—	—
5	—	—
6	—	—
7	1	1
8	2	1
9	3	2
10	4	2
11	—	4
12	1	1
13	1	1
14	1	2
Total	13	14
Arithmetic mean	9.22	10.71

measured the size of induration (Table 5). No significant difference could be shown between the two groups in the mean size of indurations.

Tuberculin allergy produced by BCG vaccination was measured after six weeks (Table 6). The smallest tuberculin reaction in each group was 7 mm of induration, the largest 14 mm, with a mean size of 9.9 mm for the thirteen light-treated children and 10.7 mm for the fourteen controls. As the small difference between the two means is not statistically significant, these findings indicate that no effect on the development of post-vaccination allergy could be demonstrated.

Discussion

Among children attending the ambulatory light therapy clinic at the Finsen Institute, no difference in the mean size of induration to the Mantoux 5 T. U. tuberculin test could be shown after five weeks between a group of eleven children receiving a routine course of carbon-arc light therapy and a group of sixteen children similarly exposed to a "control" apparatus. At the Refsnæs Coast Hospital, comparison of thirteen light-treated children with fourteen controls, all of whom were negative to Mantoux 10 T. U. prior to vaccination, showed no significant difference between the two groups in the mean size of vaccination lesions or in the size of tuberculin reactions six weeks after vaccination.

It is important to recognize certain conditions and limitations of these results. First, the size of induration of the tuberculin reactions and vaccination lesions *per se* cannot be regarded as measurements of immunity to tuberculosis, although they may be gross, indirect indices of immunity. Second, the carbon-arc treatments were not specifically directed to the anatomical sites where the tuberculin or the vaccine was injected. Accordingly, the effect of the light might be expected primarily to be due to general, systemic bodily changes. Direct exposure of vaccination lesions to intense natural or artificial light, for example, might have an effect on both the development of post-vaccination allergy and the lesions. Third, although it is not known at the present time how the dose and character of carbon-arc

light compares with natural sunlight, it may be assumed that the dose and duration of the artificial heliotherapy was relatively much less than the sum total of exposure which some children get from actual sunshine in some countries. Fourth, only a few children were studied and, considering the large experimental error inherent in the measurements made, it could not be anticipated that slight changes would be demonstrable. Changes of a sufficient magnitude to be significant for most practical work, if present, should have been found, and it may, therefore, be concluded that the routine course of carbon-arc light therapy currently in use apparently has little effect on the size of tuberculin reactions or on the development of local lesions following BCG vaccination.

Conclusions

The investigations reported in this paper gave essentially negative results. Universal carbon-arc light treatment in the doses generally administered for therapeutic purposes in this country (i. e., in series of 20—30 irradiations lasting 1/2 hour each) could not be shown to influence the formation of tetanus antitoxin after injection of tetanus prophylactic. Similarly, carbon-arc treatment had no demonstrable effect on tuberculin sensitivity in naturally-positive persons, nor on the development of local lesions and tuberculin allergy after vaccination with BCG. These latter investigations among humans confirm HELMS' work in guinea-pigs in 1935 (27), whereas the former do not agree with the results of an investigation by WILDFÜHR in 1950 (14) concerning formation of diphtheria antitoxin during light treatment.

Despite the wide-spread use of light therapy, there is disagreement among clinicians concerning its protective effect against infection. Further, the recent literature pertaining to this subject contains no conclusive evidence for the beneficial effect of light therapy. Aside from the bacteria-destroying power of ultra-violet light where, according to the literature, the maximal effect is about 2600 Ång., almost nothing seems to be known of the effect of light on the mechanism of response to infection in humans. In a very carefully conducted series of trials by DOWNES, 1950 (28),

children in two similar towns in USA were observed for three years. No difference could be demonstrated in the frequency of upper respiratory tract infections, despite the fact that in one town ultra-violet irradiation was given in schools, Sunday schools, churches, libraries, cinemas and public clinics, while in the other town there was no such irradiation. RONGE (29) reported no change in the frequency or duration of diseases of the upper respiratory tract in school children who were regularly subjected to irradiation with ultra-violet light, but he did find that these children had cardiovascular signs of greater physical capacity.

The assumption may not be warranted that because ultra-violet light is capable of killing bacteria in the laboratory, it may also be able to influence the course of infection within the human body. It is realized, of course, that the investigations reported here do not invalidate this assumption, since they reveal nothing concerning the course of infections in children during light treatment. However, clinical investigations of upper respiratory tract infections, as mentioned previously, have been in progress for some years and are still proceeding at the Finsen Institute.

There are, nevertheless, other fields where the beneficial effect of light would seem to be well-founded (in this paper no consideration is given to the well-known influence of light on calcium-phosphorus metabolism with its consequent significance for the treatment of rachitis). RONGE's investigations were interpreted to show a greater physical capacity in irradiated persons, and FINSEN's primary and encouraging observations dealt with the neuro-muscular system of laboratory animals during irradiation with different parts of the spectrum. SONNE'S and HAXTHAUSEN's (30 & 31) investigations provided evidence for the occurrence of heat hyperaemia, and LEHMANN's (32) results pointed in the same direction. Capillary microscopic examinations (DA RIVA) (33) and oxygen reduction determinations, both of which can be carried out nowadays with a much improved technique than in the first 25 years of the century, might contribute further information. As previously mentioned, it is apparent that accurate dosimetry is an absolute condition for further scientific investigation of the biological effect of light.

Summary

A firm biological foundation for the beneficial effect of carbon-arc light treatment is still lacking. Based on the assumption of a protective effect against infection, the investigations reported in this paper concern the production of antibodies in children during treatment with universal carbon-arc light. Parallel control groups, treated with light of an indifferent ultraviolet content or with no light at all, were used in the studies. The formation of tetanus antitoxin after immunization with the usual doses of tetanus prophylactic could not be shown to be influenced by carbon-arc light treatment. Neither was it possible to influence the tuberculin sensitivity of naturally positive persons, nor the development of local lesions and tuberculin allergy after vaccination with BCG. Attention is drawn to investigations concerning the neuro-muscular system, physical capacity, and metabolic variations, as possibly being fruitful spheres for continued study, and strong emphasis is laid on the absolute necessity of accurate dosimetry in future scientific investigations concerning the biological effect of light.

L'effet de la lumière à arc carbonique universel sur le développement de l'immunité.

Une fondation biologique qui permette de bénéficier de l'effet d'un traitement par la lumière à arc carbonique manque encore. Fondées sur l'hypothèse d'un effet protecteur contre l'infection, les expériences rapportées dans cet article concernent la production d'anticorps chez les enfants, durant un traitement par la lumière à arc carbonique universel. Des groupes de controle parallèles, traités avec une lumière d'une teneur indifférente en ultra-violet, ou sans lumière du tout, ont été utilisés dans cette étude. La formation d'antitoxine tétanique, après immunisation avec la prophylaxie antitétanique aux doses habituelles, ne semblerait pas être influencée par le traitement par la lumière à arc carbonique. Il ne fut pas possible non plus d'influencer la sensibilité tuberculinique des personnes naturellement positives, ni le développement des lésions locales et de l'allergie tuberculinique après vaccination au BCG. L'attention est attirée sur des expériences concernant le système neuromusculaire, la capacité physique et les variations métaboliques: il est possible que ce soit des domaines fructueux pour la poursuite de ces études, et on insiste très fortement sur la nécessité absolue d'une dosimétrie exacte dans les futures expériences scientifiques concernant l'effet biologique de la lumière.

Der Einfluss von Kohlenbogenlichttherapie auf die Entwicklung der Immunität.

Eine sichere biologische Grundlage für den günstigen Einfluss der Kohlenbogen-Lichtbehandlung fehlt bisher. Von der Annahme eines schützenden Effektes gegen Infektionen ausgehend, betreffen die hier dargestellten Untersuchungen die Produktion von Antikörpern während der Behandlung mit Kohlenbogenlicht. Parallele Kontrollgruppen, mit indifferentem Ultraviolettlicht oder ohne Lichtbehandlung, wurden zu diesen Untersuchungen herangezogen. Ein Einfluss auf die Bildung von Tetanus-Antitoxin nach Immunisierung mit den üblichen Dosen der Tetanusprophylaxe durch Lichtbogenbehandlung konnte nicht erwiesen werden. Es war weder möglich, die Tuberkulinallergie natürlich infizierter positiver Personen zu beeinflussen, noch die Entwicklung der lokalen Veränderungen und der Tuberkulinallergie nach BCG-Impfung. Die Aufmerksamkeit wird auf Untersuchungen des neuromuskulären Systems, der physikalischen Leistungsfähigkeit und der Stoffwechselveränderungen gelenkt, die möglicherweise fruchtbare Bereiche für weitere Studien eröffnen. Hervorgehoben wird die unbedingte Notwendigkeit einer genauen Dosimetrie für zukünftige Untersuchungen über biologische Lichteffekte.

Efecto de la terapéutica con lámpara de arco voltáico sobre el desarrollo de la inmunidad.

Un conocimiento biológico sólido de los beneficios de esta terapéutica es todavía necesario. Basados sobre el efecto protector frente a la infección los autores investigan en este trabajo la producción de anticuerpos en niños sometidos a esta terapéutica. Grupos de control testigos tratados con radiaciones de un contenido indiferente en radiaciones ultravioletas o sin tratar, han sido empleados en estos estudios. La formación de antitoxina tetánica obtenida tras la inmunización con dosis habituales profilácticas no ha mostrado que fuera influenciada con la terapéutica por radiación. Tampoco seddemostró una influencia sobre la sensibilidad tuberculínica de personas positivas ni sobre el desarrollo de las lesiones locales o de la alergia tuberculínica tras la vacunación con BCG. Se llama la atención sobre las investigaciones concernientes hacia el sistema neuromuscular, capacidad física y variaciones metabólicas como posibles esferas de éxito para continuar estos estudios, y se recalca la absoluta necesidad de tener en cuenta la dosificación en futuros trabajos de investigación concernientes al efecto biológico de la luz.

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FROM THE UNIVERSITY CHILDREN'S CLINIC, HELSINKI
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Observations on the Cerebrospinal Fluid in Infantile Diarrhea

by

NIILO HALLMAN and **HILKKA TÄHKÄ**

It is known that cerebral manifestations are sometimes found in infantile diarrhea, particularly in its more severe forms (YLPPÖ). Nevertheless, patho-anatomic findings yielded by the central nervous system of cases with a fatal outcome are as a rule relatively scarce (THIEMICH, MÜLLER and MANECATIDE), although some investigators have found encephalitic changes (ECKSTEIN, GOLDZIEHER, CHRISTENSEN and BIERING-SØRENSEN). Pleocytosis and increase of protein have been found in the liquor in infantile enteral infections produced by Shigella and Salmonella (KRAMÁR, MISKOKZY and CSAJÁGHY, UJSÁGHY, AGNESE). In his lecture delivered at the congress of 1947, SIWE said he had found pleocytosis and increase of protein in approximately one half of the 75 toxic patients examined by him.

We feel justified in publishing our series of 211 cases of diarrhea with different degrees of severity, because of the abundant findings deviating from the normal.

Material

The series comprised 211 patients aged from 2 weeks to 2 years who were admitted to the Children's Clinic because of diarrhea during the period from October 1950 to June 1951 inclusive. The material was not selected in any particular way. It includes both severe and mild cases, the majority of the latter having often been admitted mainly because of social circumstances. In dealing with the cases, they were grouped as follows according to symptoms and course of the disease:

Severe cases: on admission, clinically severe dehydration, unconsciousness or at any rate markedly drowsy and in several cases convulsions. All these patients were kept on parenteral therapy for one or more days. In several cases continuous intravenous infusions were given, others were treated by repeated intravenous infusions. This group included 47 cases, 6 of whom died.

Cases of moderate severity: on admission, clinically pronounced dehydration, transient disorders of consciousness in some cases. Parenteral therapy was given as a few repeated intravenous infusions. Convalescence was generally slow. Moreover, this group contained a number of young infants who made a slow recovery without needing any intravenous therapy. This group included 72 cases.

Mild cases: all other patients admitted with diarrhea. This included 87 cases.

Chronic cases: this group included the remaining 5 cases with diarrhea of the coeliac type.

Therapy: in the severe and moderately severe cases fluid therapy containing potassium was administered more or less in accordance with DARROW's recommendation. Breast-milk in gradually increasing amounts was used in these cases in the routine manner. Mild cases were treated solely by diet. — No special routine was followed in the administration of antibiotics.

Method

In all cases without exception lumbar puncture was performed immediately on admission and repeated at least twice at 3 to 4 days' intervals. If the findings were abnormal, the lumbar punctures were continued. In some cases who died there was no time to perform more than two punctures.

A cell count was carried out on the spinal fluid, and if this was found to exceed 20 cells per cmm, a differential count was made. In addition, the Pandy and Nonne protein reactions were examined. The red blood count was also carried out regularly, and if erythrocytes were abundant, the specimen was disregarded. The liquor of each patient was examined bacteriologically (i. e., stained by methylene blue and cultured in a liquid and on a solid medium). These were immediately placed into the incubator. If cells were abundant, bacterial staining and cultures were performed repeatedly.

Results

Table 1 shows all our cases grouped according to the degree of severity. In each case only that examination which revealed

Table 1

The highest observed number of cells in the spinal fluid in different cases.

Number of cells in cmm of C. S. F.	Severity of illness				Total number of cases
	Severe	Moderate	Mild	Chronic	
0—5	15 (3)[1]	34	48	3	100
6—10	6 (1)	9	15	—	30
11—20	11 (1)	13	11	—	35
21—50	6	11	11	1	29
51—100	2 (1)	4	1	—	7
> 100	8	1	1	1	11
Total					
0—5	15 (3)	34	48	3	100
> 5	32 (3)	38	39	2	111
Total number of cases	47 (6)	72	87	5	211

[1] Deaths.

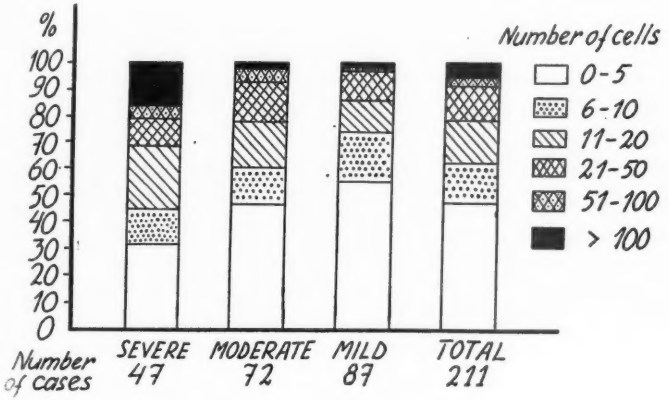

Fig. 1. The percentage distribution of cases according to the number of cells in spinal fluid.

the highest cell count was tabulated. Of the 211 cases examined, 111 had more than 5 cells in cmm at some stage of the disease, and of these 81 cases had a count exceeding 10 per cmm. Positive findings were more frequent in severe forms of the disease than in mild cases, but as shown in Fig. 1 where the C. S. F. findings are expressed in per cent, the cell count was increased fairly often even in mild cases. However, there was an obvious increase in the cell counts of the severe cases.

As described previously, a lumbar puncture was done immediately on admission of the patient and repeated after a few days. The first puncture revealed an increased number of cells in 33 cases, with an approximally similar proportion among severe, moderately severe and mild cases as that seen in the whole series. An increased number of cells was found more than once in 63 cases, and their proportion according to degree of severity corresponds to that already mentioned. It is, however, possible to entertain the opinion that the previous lumbar puncture was one of the causes responsible for the increase of cells in some of the cases. It is a well known fact that various manipulations are apt to irritate and to increase the number of cells (HALLMAN and KALLIALA, etc.), but in any event, a mere diagnostic lumbar puncture is a very weak irritant.

Table 2 includes all those punctures in which a differential count was performed. As already mentioned, this was carried out only in those cases where there were 20 or more cells. It is noteworthy that the majority of cells were lymphocytes. In only 5 of 80 examinations did the granulocytes exceed 50 per cent, in most cases they remained below 25 per cent.

Table 3 presents a comparison between the protein content of the spinal fluid determined by the Nonne and Pandy reactions, and the number of cells. The general trend seems to be that the higher the cell count, the more frequent the positive protein reactions. Naturally there are some exceptions, but if the number of cells exceeded 20, the Pandy reaction at least was regularly positive. It was a very common occurrence to find that the protein reactions were positive in spite of a normal cell count. Thus in 94 of the specimens examined both Nonne and Pandy reaction

Table 2

Lymphocytes in per cent of all leukocytes in the spinal fluid. Figures contain all punctures in which differential counts were made.

Number of cells	Lymphocytes in per cent					Total number of counts (47 cases)
	0—25	26—50	51—75	76—90	91—100	
21— 50	—	—	12	14	11	37
51—100	—	1	5	7	6	19
> 100	—	4	7	8	5	24
Total	—	5	24	29	22	80

Table 3

Protein reactions and number of cells in all punctures.

	Number of cells in cmm of C. S. F.						Total		
	0—5	6—10	11—20	21—50	51—100	>100	0—5	>5	
Nonne — Pandy —	161	18	9	—	—	—	161	27	188
Nonne — Pandy +	103	42	25	19	2	1	103	89	192
Nonne + Pandy +	94	38	43	32	20	23	94	156	250

were postive while the cell count remained below 5 per cmm. There were 42 cases in which the cell count was normal during the whole time, but Pandy was positive at some stage of the disease, and 45 cases in which Nonne and Pandy were positive at least once. Among the 211 cases of the series, there were only 13 which were always negative both in regard to number of cells and proteins.

Bacteriological findings were negative in all specimens. Changes in the cerebrospinal fluid were somewhat more general in the

younger infants, but if we consider that the most severe cases usually belong to these particular groups, it is difficult to assess to what an extent the results are affected by age as such.

The comparison between the cell findings and the general condition of the child, the weight on admission being taken as indicator shows that those cases which had a weight clearly below the normal, had somewhat more often an increase in their cell count. However, this relation is not marked in any way. In addition factors, such as the severity of the dehydration which could not be properly assessed merely by weight on admission, must be taken into consideration.

Determinations of the alkali reserve were carried out on admission in 93 cases. This included all the severe cases, more than half of the moderately severe and a few mild cases. There was no clear relation between acidosis, determined on the basis of the alkali reserve, and the number of cells. A normal cell count could be found even in such cases which showed an alkali reserve below 20 vol %.

Bacteriological examination of the feces was performed in all cases immediately on admission. Mucous membrane culture was made on a liquefying medium (selenite) and solid dish (blood-agar) and these were immediately placed into an incubator. A more detailed bacteriological examination was performed at the State Serum Laboratory (RANTASALO). In addition, serological examinations were carried out on each patient. In *Table 4* the cases are grouped according to the probable causative agent. The so-called miscellaneous group contains cases from the feces of which the following bacteria were grown: proteus, common escherichia, pseudomonas aeruginosa, enterococcus etc., and it is impossible to say what role is played by each of them in the genesis of diarrhea. From this group we segregated cases produced by s. e. Dyspepsia coli. This coli group includes the so-called neapolitana strain, as well as some other strains determined by the Kaufmann laboratory. A special group was formed by Shigellas serological findings (FLEXNER, SONNEI). There was not a single instance of Salmonellae. It is evident that C. S. F. changes are most frequently found in diarrhea produced by Shigellas, and the

Table 4

Deviation from the normal cell count grouped according to the cause of diarrhea.

	Number of cells		Total number of cases
	0—5	>5	
Shigella (Sonnei, Flexner)	12	23	35
Dyspepsia coli	9	5	14
Miscellaneous bacteriae	79	83	162
Total	100	111	211

majority of these patients did not belong clinically to the most severe group. Changes in the miscellaneous group were also more frequent than in the so-called dyspepsia coli group, even if this latter contained a considerable number of grave cases. However, the group is too limited to allow a reliable comparison.

A number of patients exhibited, apart from diarrhea, marks of other infections and these are set out in Table 5. No clear difference could be found. Yet it is noteworthy that all those

Table 5

The role of other infections.

	Number of cells		Total number of cases
	0—5	5	
Cough and cold	20	18	38
Bronchitis	12	13	25
Pneumonia	9	14	23
Pneumonia and empyema pleurae	3	2	5
Otitis media suppurativa	—	3	3
Urinary infection	1	3	4
Skin infection	5	5	10
Pure diarrhea	50	53	103
Total	100	111	211

three cases which were affected with suppurative otitis media had an increased cell count. However, the number of cases was only three and all recovered without any special therapeutic measures.

Discussion

As reported above, changes in the spinal fluid were strikingly frequent. Increased cell counts were found in at least one specimen in 111 of the 211 cases, and in addition, there was an increase in the protein in 87 cases, so that in only 13 cases was the C. S. F. completely normal. In the majority of specimens the cells were mainly lymphocytes. Bacterial stainings and cultures from the spinal fluid were negative without exception.

Pleocytosis and an increase in the protein have been found in a great number of infantile infectious diseases, particularly when the patient exhibits meningeal symptoms (BLATTEIS and LEDERER, LEVINSON). In severe diarrhea, so-called "toxicosis", symptoms produced by the central nervous system are a constant feature, and therefore positive findings both as regards proteins (RAPOPORT *et al*). and cells (SIWE) are easy to understand. Our series demonstrates that changes in the C. S. F. can be found even when the diarrhea is mild, without any signs of cerebral irritation. It is true that changes are more frequent and also more marked in severe cases, but even so, this is not a rule without exception.

Cases of diarrhea produced by the Shigellas have shown changes in the C. S. F. similar to those reported by us (KRAMÁR *et. al.*, UJSÁGHY). In our series we also found pleocytosis to be more frequent in these cases than in others with an unknown etiology. However, the difference is not great, if consideration is also given to the increase in the protein. Nor can it be maintained that infections of the respiratory tract, when occurring simultaneously with diarrhea and indicating influenza of some kind, should affect the results in any significant way.

It has been demonstrated, by using different colour substances, that even normal infants (LEONEW) and especially premature babies (OTILA), have an increased meningeal permeability. Marked changes are also found in several infantile diseases, in particular,

in toxic diarrhea (LEONOW, BESSAU and ROSENBAUM, ROSENBAUM, SCHAFERSTEIN). The whole toxic condition in which dehydration (MARRIOT) plays a considerable part, has been explained as due either to released coli toxins (BESSAU), or to the effect of amines (MORO) on the central nervous system. In a way, the French so-called neuro-toxic theory (ROHMER *et al.*, VERGER) can be placed into this same group.

Pleocytosis in the C. S. F. found by us cannot be directly compared with the increased permeability, but a parallel can be drawn with the increase in the protein, which SCHAFERSTEIN considers a poorer standard for measuring increased permeability than staining tests.

In recent years there has been a considerable rise in the incidence of severe infantile diarrhea in Finland (LOUHIVUORI and NEVANLINNA, YLPPÖ *et al.*), but during the period covered by this investigation it was becoming less severe. It is of course conceivable that the undknown causative agent of this diarrhea had a specific effect on the central nervous system and that the abundant positive findings in the spinal fluid, even in non-toxic cases, can be attributed to this effect. However, studies of simultaneous post-mortem material (HALLMAN and AHVENAINEN) agree with scare findings in the central nervous system of diarrhea patients reported by earlier investigators.

In assessing the results, the fact must be considered that changes in the C. S. F. were not always found in the first puncture. Since we know how sensitively the spinal fluid can react to certain manipulations (HALLMAN and KALLIALA), it is conceivable that part of the positive findings can be due to irritation produced by the preceding puncture.

It is, however, evident that our results indicate that even mild diarrhea is not merely an intestinal disease, instead, it is a more generalized condition.

Summary

1. A study of the cells in the spinal fluid, as well as Nonne and Pandy reactions, was made in 211 cases of infantile diarrhea of various degree of severity. — 2. The number of cells in C. S. F. was invariably (2—4 examinations) below 5 per cmm in 100 cases, and it was found to

be increased at least once as follows: 6—10/cmm in 30 cases, 11—20/cmm in 35, 21—50/cmm in 29, 51—100/cmm in 7, and over 100/cmm in 11 cases. The changes were generally more extensive in the severe cases, but the difference between them and the mildest cases which did not exhibit any symptoms pertaining to the central nervous system, was not particularly significant. — The majority of the cells were diagnosed as lymphocytes. — 3. If the protein reactions are also taken into consideration, the spinal fluid was found within normal limits in only 13 patients. — 4. The age at onset, the weight of the infant as compared with the expected weight, the alkali reserve on admission and other simultaneous infections do not seem to have any noteworthy effect on changes in the spinal fluid. — 5. Changes were found to be more frequent in diarrhea produced by the Shigellas (35 cases) than in other cases due to an unknown causative agent. — 6. Bacterial staining and culture of the C. S. F. were negative in all cases.

Observation du liquide céphalo-rachidien dans la diarrhée infantile.

1. Une étude des cellules dans le liquide céphalo-rachidien, ainsi que des réactions de Nonne et de Pandy a été faite dans 211 cas de diarrhée infantile, de divers degrés de sévérité. — 2. Le nombre de cellules dans le liquide céphalo-rachidien était invariablement (2 à 4 examens) au-dessous de 5 par cmm dans 100 cas, et on l'a trouvé augmenté au moins une fois, comme suit: 6—10/cmm dans 30 cas, 11—20/cmm dans 35, 25—50 dans 29, 51—100 dans 7, et au-dessus de 100 dans 11 cas. Les modifications étaient généralement plus étendues dans les cas sévères, mais la différence entre eux et les cas plus bénins, qui ne présentaient pas de symptomes d'atteinte du système nerveux central, n'était pas particulièrement significative. La majorite des cellules ont été diagnostiquées comme lymphocytes. — 3. Si les réactions albuminiques sont aussi prises en considération, le liquide céphalo-rachidien a été trouvé négatif chez 13 malades seulement. — 4. L'âge au début, le poids de l'enfant comparé au poids idéal, la réserve alcaline à l'entrée et d'autres infections simultanées ne semblent pas avoir quelque effet important sur les modifications du liquide céphalo-rachidien. — 5. Des modifications ont été trouvées plus fréquemment dans des diarrhées produites par le bacille de Shiga, que dans d'autres cas dûs à un causal inconnu. — 6. La recherche directe de bacilles dans le liquide céphalo-rachidien, ainsi que la culture, ont été négatives, sans exception.

Untersuchungen über die Spinalflüssigkeit bei kindlicher Diarrhoe.

1. Eine Studie der Liquorzellen, der Nonne- und Pandyreaktion bei 211 Fällen kindlicher Durchfallserkrankung verschiedener Schweregrade wurde durchgeführt. — 2. Die Zellzahl im Liquor war unverändert (bei

2—4 Untersuchungen) unter 5 pro cmm in 100 Fällen und wurde (mindestens einmal) erhöht gefunden, wie folgt: 6—10/cmm in 30 Fällen, 11—20/cmm in 35, 21—50/cmm in 29, 51—100/cmm in 7 und über 100/cmm in 11 Fällen.

Im allgemeinen waren die Veränderungen ausgedehnter in schwereren Fällen, aber der Unterschied zwischen diesen und den leichtesten Fällen, welche keine auf das Zentralnervensystem hinweisenden Symptome boten, war nicht significant. Die Mehrzahl der Zellen wurde als Lymphocyten angesprochen. — 3. Wenn die Eiweissreaktionen mit in Betracht gezogen werden, war der Liquor nur bei 13 Patienten normal. — 4. Alter bei Beginn, Gewicht des Kindes im Vergleich zur Norm, Alkalireserve bei der Aufnahme und Zusammentreffen mit anderen Infektionen schienen keinen wesentlichen Einfluss auf die Veränderungen des Liquors zu haben. — 5. Veränderungen wurden häufiger gefunden bei Diarrhoen durch Shigella (35 Fälle) als bei Fällen unbekannter Ätiologie. — 6. Bakteriologische Färbungen und Liquorkulturen waren ausnahmslos negativ.

Observaciones sobre el líquido céfalorraguideo en las diarreas infantiles.

1. En 211 casos de diarreas infantiles de diverso grado de severidad se hace un estudio de las células del líquido cefalorraquideo así como de las reacciones de Nonne y Pandy. — 2. El número de células era invariable (2—4 exámenes) por debajo de 5 ccm en 100 casos y se encontró aumentado en las siguientes proporciones: 6—10/cmm en 30 casos, 11—20 en 35, 21—50 en 29, 51—100 en 7, y mas de 100 en 11 casos. Las alteraciones eran generalmente mas amplias en los casos severos, pero la diferencia entre estos y los de mediana gravedad que no presentaban síntomas en relación con el sistema nervioso central no eran particularmente significativas. La mayoría de estas células eran identificables como linfocitos. — 3. Si se tienen en cuenta las reacciones de proteinas el líquido cefalorraquideo era negativo tan solo en 13 casos. — 4. La edad de comienzo, el peso del niño en relación con el peso ideal, la reserva alcalina en el momento de admisión u otras infecciones simultáneas que pueiera haber no han mostrado tener ningún efecto evidente sobre las alteraciones del liquido cefalorraquideo. — 5. Las alteraciones se mostraron mas frecuentemente en las diarreas producidas por shigelas (35 casos) que en otros casos de etiología por agente desconocido. — 6. Los frotis para el exámen bactereológico y los cultivos del liquor fueron siempre negativos sin excepción.

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The Relation of Breast Feeding Prognosis to the Initial Amount of Maternal Milk

by

GERT v. SYDOW

One of the main problems for a pediatrician caring for newborn babies in a lying-in hospital is, what to tell a mother about to be discharged from the hospital concerning her future ability to feed her child; and what can be done at the hospital in order to improve this ability. It is very important, in my opinion, that she gets reliable advice on this point: it helps her to avoid many risks menacing breast feeding especially in the early weeks, and takes away from her mind many unnecessary fears. It may also increase her confidence in those authorities who are going to give her advice on infant feeding later on.

Among the many investigations made on factors influencing the duration of lactation hardly any deal with the possibility of predicting the outcome from information already available at the obstetric hospital. In the individual case, however, there are sometimes factors present which definitely condemn the prognosis of lactation. Thus, it goes without saying that a child who is going to be adopted, or who will be immediately admitted to an Infant's Home, will not be breast fed for a very long time. It is also evident that the prognosis is considerably deteriorated if the infant is born with a cleft palate or heart failure, or if the mother's nipples are retracted, if these failings, or their effects, cannot be removed. But what guidance can be obtained where there are no obvious digressions from normal?

Obviously, the infant's neonatal weight curve can give no guidance. The initial loss of weight does not seem to be very much

influenced by the amount of food ingested, but rather by the water content of the infant's body at birth. It may, however, influence the prognosis of breast feeding in so far as the infant may happen to be prescribed an unnecessary food supplement only because it has not regained its birth weight at, for example, one month of age — an occurrence which should be prevented.

It remains, then, to be examined if the amount of milk produced during the puerperium can give any assistance in predicting the outcome of lactation. It seems plausible that mothers who yield an ample supply of milk at the start of lactation will also do so in the future, since this ample yield at the start indicates a good functioning glandular apparatus and may increase the mother's confidence in her own nursing capacity, and possibly also prevent those discomforts or even the aversion against nursing which sometimes accompanies a scanty milk secretion. This makes one believe, that it would to a certain degree be possible to improve the prognosis of lactation by measures leading to an increased initial production of milk.

In order to do this, the plan was adopted at the obstetric departments in Gothenburg that, after the child had suckled its five meals a day, each time on both breasts, the breasts should be compulsorily emptied manually at least four times a day. By this we wished to bring about a certain surplus of milk in as many mothers as possible on leaving the hospital which, we hoped, would lessen the temptation of early weaning. That in a great many cases we succeeded in increasing the production of milk above the needs of the child turns out from the fact that the obstetric departments yielded, on an average, 20 liters of breast milk daily throughout the year to the breast-milk bank.

By aid of the Children's Welfare Centres of Gothenburg an inquiry has now been made about the success of breast feeding in those infants discharged from the obstetric departments to their homes in the city during the half year period (Sept. 1946—Febr. 1947, incl.). Those infants who were discharged from the hospital to other hospitals, to infants' homes or to foster homes, and infants who could not be identified in the records of the Centre to which they were entered from the obstetric department were

excluded from the investigation. Those infants who died during the observation time, and also those who had moved from their original Welfare Centre before two months of age were also excluded. Those who moved after two months of age were included, and, if they were breast fed on the removal, they were reckoned as breast fed for as long a time as they stayed in the original centre. The series was also limited to include only infants with a birth weight of 3 000 grams or more and also those who were not born in multiple births. Finally those infants in the obstetric department who had been found to suffer from defects which could then already be claimed to considerably deteriorate their breast feeding prognosis were excluded: — e. g., mongolism, heart failure, cleft palate. On the other hand, infants with diseases which could not have been anticipated at the hospital were not excluded, e. g., infants with pyloric stenosis or severe infections, nor were infants where it could probably be anticipated that the lactation would be rendered difficult by defects in the mother — as far as it was not definitely delayed before discharge — because it was felt that the selection might then have been rendered subjective — it is not easy, for a pediatrician at least, to prognose on the outcome of a cracked nipple or a maternal psychoneurosis.

This series, which by these measures was limited to *1 838 infants*, then comprises all infants with a birth weight not below 3 000 grams, born in single births at the obstetric departments in Gothenburg during six months, and which have been discharged with their mothers to their homes in the city, who have belonged to the same Children's Welfare Centre until the age of at least two months, who have not died before nine months of age, and who had not been found at the obstetric department to suffer from any severe defect which might hazard breast feeding.

The period of breast feeding has been reckoned all the time during which the baby had been partly or totally nursed at the breast, according to the records of the Welfare Centre. Where it was difficult to determine whether a figure meant the total period of breast feeding or the period of exclusive breast feeding, it was decided that it would mean the total period. Obviously, there was a risk that cases would in this way be included where breast

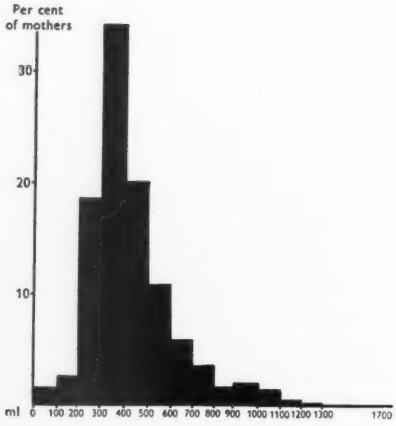

Fig. 1. Quantity of milk on the sixth day of puerperium.

feeding for a certain time was merely "symbolic" and of no importance for the infant's nutrition, but it was felt that the number of such cases must be very small in this series.

As a basis for comparison the milk production on the infant's sixth day of life was chosen. This was the latest day that could be chosen because many mothers were discharged on the seventh day. It appears from Fig. 1 that the secretion was well started at this time in by far the majority of cases. The frequency curve is very steep with the median at 382 ml and the first and third quartile border at 310 and 496 ml respectively. More than half the mothers then had between 300 and 500 ml of milk on the sixth day while one fourth had less than 300 and one fourth more than 500 ml.

In Fig. 2, which presents the duration of breast feeding, the curve is of course not as regular as in Fig. 1. There are two peaks, at 6 and 9 months, which are explained by the aims of the feeding program of the welfare centres: this has aimed at exclusive breast feeding for six months and then successive weaning during the following three months. The peak at six months probably depends partly on the fact that mothers with feeding difficulties are

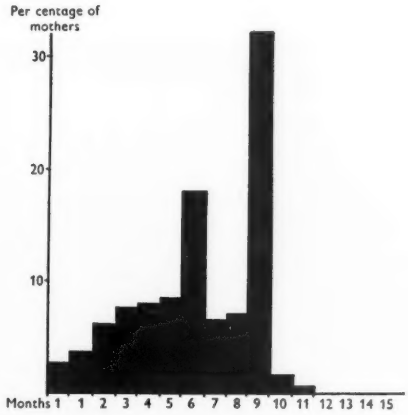

Fig. 2. Duration of breast feeding.

encouraged, if possible, to persevere until six months; in part the explanation may also be that in some cases the duration of exclusive breast feeding has been reported instead of the total duration. In the rising curve before six months most cases of hypogalactia are naturally to be found, and also many cases where the mothers have had to finish breast feeding too early because they had to work; and some mothers who had moved from their original homes from between two and six months after delivery. There are also some mothers who have nursed for more than nine months, and the number of such cases may, in reality, have been greater than stated because our inquiries have been as a rule made as soon as all infants born in a certain calendar month have reached nine months of age. These cases may include mothers with weaning difficulties, mothers who continue breast feeding as a prophylaxis against a new pregnancy, and mothers who for some reason e. g. weakness of the child, have been especially ambitious to nurse their infant. Thus, there are many factors co-operating to form this curve and it does not seem necessary to analyse it in detail. So, for the comparison, I have restricted myself to dividing it into three parts: those nursed for six months or more; those

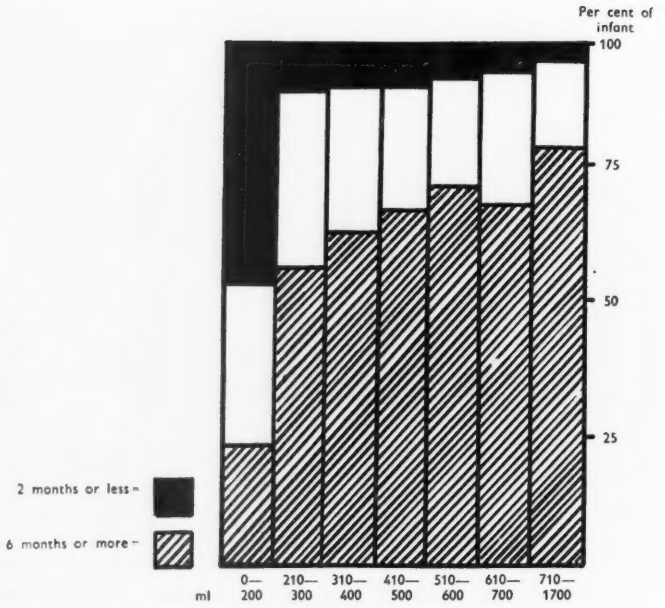

Fig. 3. Relation of duration of breast feeding to quantity of milk produced on the sixth day of puerperium.

nursed for between two and six months; and those breast fed for less than two months. Of the total series, the last-mentioned make up only 6.1 per cent; 93.9 per cent, consequently, have been nursed for at least two months. Those nursed for at least six months make 64.7 per cent, i. e. about two thirds of the total series.

Now about the correlation between duration of breast feeding and initial amount of milk, it appears from Fig. 3 that the duration of breast feeding is, on the whole, increasing with an increasing amount of milk on the sixth day of life. There is a large difference especially between the first column, representing those yielding 200 ml of milk or less on the sixth day, and the rest of the diagram. In the first group, no less than 44.1 per cent were weaned before two months of age; while the corresponding figures vary between 6.6 and 0.6 per cent in the following groups. Conversely; in the lowest group only 22.1 per cent were breast fed for at least six

Duration of breast feeding	Quantity of milk produced on the sixth day of puerperium							
	0—200 ml	210—300 ml	310—400 ml	410—500 ml	510—600 ml	610—700 ml	710—1 700 ml	0—1 700 ml
< 2 months	30 = 44.1 % ± 6.03%	22 = 6.6 % ± 1.43%	31 = 5.0 % ± 0.89%	17 = 4.7 % ± 1.11%	9 = 4.7 % ± 1.45%	3 = 2.8 % ± 1.60%	1 = 0.6 % ± 0.20%	113 = 6.1 % ± 0.57%
2 months <	38 = 55.9 % ± 6.03%	312 = 93.4 % ± 1.43%	589 = 95.0 % ± 0.89%	345 = 95.3 % ± 1.11%	184 = 95.3 % ± 1.45%	103 = 97.2 % ± 1.60%	154 = 99.4 % ± 0.20%	1 725 = 93.9 % ± 0.57%
6 months <	15 = 22.1 % ± 5.01%	192 = 57.5 % ± 2.69%	394 = 63.5 % ± 1.93%	251 = 69.3 % ± 2.43%	140 = 72.5 % ± 3.20%	74 = 69.8 % ± 4.42%	124 = 80.0 % ± 3.20%	1 190 = 64.7 % ± 1.11%
Totals	68	334	620	362	193	106	155	1 838

Fig. 4.

months while in all the other groups more than half the infants were nursed as long as that, in the highest group no less than 80 per cent. The difference is strongly significant between the lowest group and the rest of the series, being many times higher than its standard error, but this is not the case between adjacent groups in the rest of the table (Fig. 4).

These figures, then allow us to tell a mother about to be discharged from the lying-in hospital, and whose milk production on the sixth day exceeds 200 ml, that she will have a good chance to carry through breast feeding; that there is hardly any risk for the milk to cease before the infant is two months old; and that there is a more than fifty per cent probability that she will manage to nurse it for at least six months. This can be stated all the more emphatically when the mother's milk production at the hospital is higher, and it should thereby be borne in mind that these figures include not only those mothers and infants who have had to wean because of diseases connected or unconnected with lactation, or from social reasons, but also all mothers with retracted nipples, sore nipples, mastitis, etc., even when this had already been evident at the hospital. This means that to a mother who has not had any breast troubles at the hospital, we are justified in predicting that her chances to perform lactation are still better than would appear from this table.

Can anything be done then, to improve the prognosis of breast feeding for mothers with poor initial lactation? It might seem probable that if these mothers could be persuaded to stay at the hospital until more satisfying amounts of milk were obtained, then the prognosis would become better. This, however, cannot be verified in the present series. Those mothers who stayed on at the hospital for more than the usual six days and whose milk production was increased into a higher class before discharge did not show a better prognosis than the rest of their lactation class on the sixth day. It should be borne in mind, however, that most of these mothers were not retained in hospital in order to increase their lactation output but because they were ill: they included cases of surgical deliveries, fever, toxaemia etc., and in a few cases mothers whose infants were soporous and did

not suck well. They thus comprise a selection of cases who for other reasons, would be expected to have a poor prognosis of breast feeding and this may hide the possible beneficial effects of the prolonged hospital care.

As was mentioned before, we have started with the hypothesis that the feeding prognosis could be improved by provoking a surplus of milk in the mothers on discharge, and we have therefore emptied the breasts manually after feeding in all mothers from the third day on. As a result, in most mothers there was a certain surplus, usually rather modest but in some cases quite considerable. In order to control if this really does improve the feeding results, I have now selected those cases where the surplus amounted to at least 100 ml on the sixth day, and compared them with the total group. These selected cases were found to amount to 546 mothers, i. e., nearly 30 per cent of the total series, and the mean surplus of these 546 mothers on the sixth day amounted to 278.4 ml. The comparison is illustrated in Fig. 5. The series here is divided into three groups according to the amount of milk taken by the infant: one group where the infant has itself taken a clearly sufficient amount of milk, one where it has taken a clearly insufficient amount, and a middle group. In the right group, where the infant has taken more than 300 ml, the difference is significant: Those with a surplus are much more often breast fed for more than six months and much more rarely for less than two months. Even if the surplus group should be compared here with the total group taking more than 400 ml, the values would be better, but these differences are not significant, but they are more than twice their standard errors.

In the left column, which represents those infants who sucked only 200 ml or less, the feeding prognosis is also better for those with a surplus. Because of the large standard errors in the small series the difference here is not significant for those nursed for 6 months or more, but what is worth observing is that in spite of the large standard errors the difference is significant for those nursed for two months or less. — In the middle group too, the same tendency is found but the differences here are small and not significant.

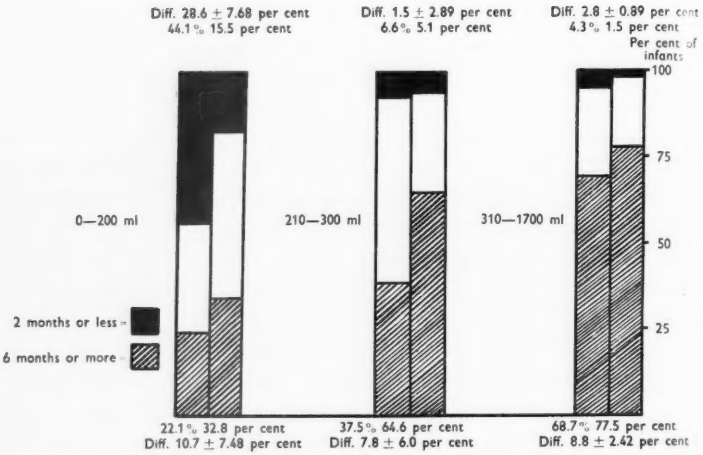

Fig. 5. Duration of breast feeding when the infant was taking different quantities of milk on the 6th day, a manually emptied surplus being (right columns) or not being (left columns) present.

What conclusions can be drawn then, from these comparisons? Obviously, it must be a little differently argued about the comparison to the right in the diagram, concerning infants who have themselves taken what may be regarded as sufficient daily rations which, however, could be further increased by the pumping, and about the infants who had not been able to obtain their need by their own sucking but where the efforts of the mother could bring about a considerable improvement. In the latter case, it is quite obvious that the pumping would be able to prolong the period of breast feeding: This group naturally comprises the debilitated infants who could not suck sufficiently to maintain lactation but where the mother could maintain it by pumping, possibly until the infant would be able to take over the task. It also comprises all cases with retracted or sore nipples where the infant was not able, or not allowed, to suck and where the mother had to act as a substitute. Probably these and similar factors will entirely explain the improvement of the prognosis in those cases where the mother is energetic enough and capable to take over the role

of the suckling. Perhaps it is no accident that the difference in prognosis here is significant only at the two-months level; in many cases probably the mother's efficacy does not suffice to carry it through also over the next level.

Concerning the large group to the right in the diagram, where the infant was able to take its reasonable needs itself on the sixth day, the better prognosis in those cases where there is beyond this a surplus available, may probably be explained in three, or perhaps four different ways. First, the manual emptying may be supposed to carry with it a real improvement in the secretory capacity of the milk glands and thanks to this the breast feeding will get along over what is called by CHARLOTTE NAISH the "danger weeks", the period immediately following the arrival home from hospital, where there seems to be in many cases a transient decrease in milk secretion; it may also possibly result in an improved secretion in the long run. Secondly, the surplus of milk may be supposed to strengthen the confidence of the mothers in their own nursing ability and in this way prevent unnecessary supplementary feeding, which might have meant the start of an early weaning. Thirdly, it may be possible that the surplus simply means that the mother in question has a good capacity for secreting milk and would, consequently, have had a good prognosis of breast feeding even if she had not been forced to empty manually. Finally the surplus may be an expression of the strong ambition in a mother to succeed with breast feeding, and may mean that she will do her best in order to carry it through in other ways too.

According to the two last-mentioned explanations the pumped surplus would then be rather a consequence of the good prognosis of breast feeding than a cause of it, but according to the two first-mentioned it would be a contributory factor to the good result. It seems difficult to decide how much importance should be accredited to the different explanations, but it seems reasonable to assume that they may all play a part. It would probably be possible to get an idea of how far the evacuation may have a causal importance by comparing this series with one where a routine emptying had not been practised, but where the feeding

routine had in other ways been identical. Until such a comparison has been made possible it seems permissible to assume that the psychical value at least of the mother being convinced that she can produce more milk than the infant will take, must be of no small importance for the prognosis of breast feeding, and therefore, routine pumping should, in our opinion, be carried out where possible.

It may be concluded then, that if a mother has been healthy during her stay at the lying-in hospital, if her nipples have been normal, if her infant is healthy and sucks vigorously, if there are no known social circumstances that would be disastrous to breast feeding — and if such a mother has produced 300 ml of breast milk or more on the sixth day after delivery, then we are justified in telling her that she will have practically a 100 per cent chance to carry through a well-managed breast feeding for at least two months, and at least a 2:1 chance to carry it through for six months or longer. Should all these pre-requisites not be present, then the prognosis deteriorates to a greater or lesser degree, and should the mother have succeeded in producing a considerable surplus of milk, then the prognosis will be better still. For the great majority of mothers leaving the lying-in hospital it is thus possible to forecast a very favourable nursing prognosis, and by telling this to a mother it may be possible to prevent some unnecessary premature weanings, thereby contributing to a still more improved prognosis.

Summary

In a series of 1 836 consecutive cases of infants with a birth weight of 3 000 g or more, who had not shown any manifest defects during the first week of life and who after discharge with their mothers to their homes could be followed at least to the age of two months, the duration of breast feeding was compared with the amount of milk produced by the mother on the infant's sixth day of life. Duration of breast feeding was reckoned as the total time until the infant was definitely weaned from the breast. Those infants where the mother had delivered 200 ml of milk or less on the sixth day suffered considerably shorter periods of breast feeding than the rest, 44.1 per cent being weaned before 2 months of age against 6.6—0.6 per cent in the other groups, and only 22.1 per cent

being breast fed for at least 6 months, as against 50—80 per cent in the groups with higher initial lactation. Those infants where the mother had been able to pump out at least 100 ml of milk beyond what the infant had sucked itself, were breast fed for a considerably longer time than the mean of the total series, and this applies to the group where the infant had been able to suck itself at least 300 ml as well as to the group where the infant had sucked not more than 200 ml. It seems, therefore, as if it would be possible to improve the prognosis of breast feeding in many cases by regular manual emptying of the breasts.

La relation entre le pronostic de l'allaitement au sein et la quantité initiale de lait maternel.

Dans une série de 1 836 cas consécutifs de nourrissons avec un poids de 3 000 gr. ou plus, qui n'ont pas montré quelque déficience manifeste pendant la première semaine de leur vie, et qui, après retour avec leurs mères à la maison, ont été suivis au moins jusqu'à l'âge de 2 mois, la durée de l'allaitement au sein a eté comparée à la quantité de lait produit par la mère pendant le sixième jour de vie de leur nourrisson. On compte comme durée de l'allaitement au sein le temps total écoulé jusqu'au sevrage définitif du nourrisson. Les nourrissons, dont les mères ont fourni 200 ml de lait ou moins, pendant le sixième jour, reçoivent l'allaitement au sein pendant des périodes considérablement plus courtes que les autres: 44.1 % sont sevrés avant 2 mois, contre 6.6—0.6 % dans les autres groupes; seulement 22.1% sont nourris au sein pendant au moins 6 mois, contre 50—80 % dans les groupes avec lactation initiale plus élevée. Les nourrissons dont les mères ont été capables de pomper au moins 100 ml de lait, en sus de ce qu'ils ont têtés eux-mêmes, ont été nourris au sein pendant un temps beaucoup plus long que la moyenne de toutes les séries. Ceci s'applique au groupe de nourrissons qui ont été capables de têter eux-mêmes au moins 300 ml, aussi bien qu'à ceux qui n'ont pas têtés plus de 200 ml. Il semble donc qu'il serait possible d'améliorer le pronostic de l'allaitement au sein dans de nombreux cas, par le vidage manuel régulier des seins.

Verhältnis von Brusternährungs-Prognose zu der Anfangsmenge von Muttermilch.

In einer Serie von 1 836 aufeinanderfolgenden Fällen von Säuglingen mit einem Geburtsgewicht von 3 000 gr. und mehr, welche keine Störungen in der ersten Lebenswoche erkennen liessen und die nach Entlassung mit ihren Müttern mindestens bis zum Alter von 2 Monaten kontrolliert werden konnten, wurde die Dauer der Brusternährung mit der Milchmenge der Mutter am 6. Lebenstag des Kindes verglichen. Als

Dauer der Brusternährung wurde die Gesamtzeit bis zum definitiven Abstillen bezeichnet. Jene Kinder, deren Mütter am 6. Tag 200 ccm Milch oder weniger lieferten, erreichten eine beträchtlich kürzere Stillzeit als die übrigen. 44.1 % wurden bereits vor Ende des 2. Lebensmonats abgestillt, gegenüber 6.6—0.6 % in den anderen Gruppen, und nur 22.1 % erhielten mindestens 6 Monate Brusternährung, gegenüber 50—80 % in den Gruppen mit höherer initialer Milchmenge. Jene Kinder, deren Mütter in der Lage waren, mindestens 100 ccm Milch über die vom Kind abgesaugte Menge hinaus abzupumpen, wurden deutlich länger an der Brust ernährt als der Durchschnitt der ganzen Untersuchungsreihe; dies gilt sowohl für die Gruppe, deren Kinder mindestens 300 ccm saugten, als auch für jene, deren Kinder nicht mehr als 200 ccm saugten. Es scheint möglich zu sein, die Prognose der Brusternährung in vielen Fällen durch regelmässiges manuelles Entleeren der Brüste zu verbessern.

Relación entre las cantidades iniciales de leche materna y el pronóstico de la lactancia materna.

En una serie de 1 836 casos consecutivos de niños nacidos con un peso de 3 000 gr. o mas los cuales no mostraban ninguna alteración manifiesta durante las primeras semanas de la vida y que fueron observados por un período mínimo de 2 meses, se comparan la duración de la lactancia materna con las cantidades de leche producidas por la madre durante el sexto día de vida del niño; la duración de la lactancia materna se considera como el tiempo total hasta el cual el niño era separado del pecho de la madre. Los niños cuyas madres habían producido 200 c.c. o menos de leche durante el sexto día disfrutaban de períodos de lactancia materna considerablemente mas cortos que los restantes; 44.1 % eran destetados antes de los 2 meses de edad frente a 6.6—0.6 % en otros grupos y solo 22.1 % podían ser alimentados al pecho durante un período mínimo de 6 meses frente a un 50—80 % de los grupos con lactancia inicial de valores elevados. Los niños cuyas madres eran capaces de poder extraerse como mínimo 100 c.c. de leche después que el niño había succionado en el total de las series se veía que la lactancia materna se desarrollaba durante un período de tiempo mas prolongado y ello era también aplicable al grupo de niños capaces de succionar por ellos mismos como mínimo 300 c.c. en comparación con el grupo que no succionaban mas de 200 c.c. Parecería pues posible el mejorar el pronóstico de la lactancia materna en algunos casos a través de un vaciamiento manual regular mamario.

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FROM THE PEDIATRIC CLINIC OF KAROLINSKA SJUKHUSET, STOCKHOLM, HEAD: PROF. A. WALLGREN, AND THE DEPARTMENT OF OPHTHALMOLOGY, SABBATSBERGS SJUKHUS, STOCKHOLM, HEAD: I. KUGELBERG M. D.

The Appearance of the Fundus Oculi in Premature Infants, with Special Reference to the Early Stages of Retrolental Fibroplasia

by

A. HUGGERT

Ever since TERRY'S investigations in 1942, an ever increasing interest has been shown in retrolental fibroplasia and such-like conditions in premature infants. Many works have been published about this subject especially in America (TERRY, REESE and PAYNE, KRAUSE, OWENS and OWENS, KINSEY and ZACHARIAS, HEPNER, KRAUSE, and NARDIN, SPEERT, BLODI and REESE). In spite of all efforts the aetiology remains obscure although several different theories have been put forward. Nevertheless the consequences of this eye disease are so serious that one feels that routine ophthalmoscopy should be carried out in all premature infants. This applies especially in the early stages of the disease, because this is the only stage at which something can be done. It would seem that all efforts to deal with a fully developed retrolental fibroplasia are doomed to failure, if one is to judge from the results of previous workers (TERRY, REESE, KINSEY and CHISHOLM). Besides this the results from the point of view of prophylaxis are contradictory and unconvincing (OWENS and OWENS, REESE and BLODI, KINSEY and CHISHOLM).

There are some excellent reports on the earliest stages of this disease and the best of these are by OWENS and OWENS, and HEATH. These American investigators found in the earliest stages that the retinal vessels were markedly dilated, and in the peripheral portions of the fundus there were white oedematous areas,

which were localized along the peripheral vascular branches. On the surface of these oedematous areas, one could observe numerous newly formed capillary vessels. Similar fundus findings have been reported by REESE, HOLM, REESE and BLODI, KINSEY and CHISHOLM.

OWENS and OWENS, HEATH, KINSEY and CHISHOLM, REESE and BLODI also report in some cases with these early changes, that they may recede completely irrespective of whether treatment was instituted or not. Unfortunately, however, there is no record showing the percentage of cases in which resolution took place, nor is there any clear picture in SZEWCZYK'S preliminary report. The question which arises is whether these cases are really retrolental fibroplasia at all or whether they might be a more or less normal variation of the fundus in premature infants. In newly born full-term infants the normal fundus picture is well known, e. g. SCHLEICH, KÖNIGSTEIN, STUMPF and VON SICHERER, SEISSIGER. HEATH also states that full-term infants sometimes show a grey colour in the periphery of the fundus, but never oedema or newly-formed vessels. It appears that there has never been any detailed investigation of the normal fundus of premature infants not afflicted with retrolental fibroplasia, and that therefore an investigation of this nature appears advisable.

If one studies the embryological development of the eye, one finds some support for the theory that in premature infants, deviation from the normal picture of the fundus may be found when compared with the fundi of full-term infants. The best description of the embryology of the eye appears to be by IDA MANN. One sees from her book "Developmental abnormalities of the eye", that during the whole period of pre-natal life the different layers of the fundus are not so closely connected with one another as later, so that separation of the different layers easily takes place, and especially in the poorly differentiated anterior parts of the retina. HEATH has also pointed out that the microscopic appearances in retrolental fibroplasia indicate such a separation of the different layers. He even examined stillborn prematures and found, in certain cases, a similar picture. It is to be presumed that in such cases there is a predisposition to retrolental fibro-

plasia, but that the disease doesn't become manifest until a few weeks after birth.

In November 1950 the author was asked by Professor Wallgren of the Pediatric Department of Karolinska Institutet, to examine the fundi of all premature infants having a low birth-weight with the object of being able to discover early cases of retrolental fibroplasia. Up to the present, the author has been able to examine 66 infants with a birth-weight of less than 2 600 g. In this series there were no cases of retrolental fibroplasia which is not surprising considering the smallness of the material, and the fact that the incidence of the disease in Sweden appears to be very low (BJELKHAGEN).

During the examinations the author found certain changes which deviated from the normal fundal picture as seen in full-term infants and which will be the object of a more detailed report. As retrolental fibroplasia has such a low incidence in Sweden, these findings will be of greater value when estimating the normal fundus picture in premature infants, as there will be very little risk of the picture being confused with the early stages of retrolental fibroplasia.

First one has to consider the method of examination. Most American authors appear to have used direct ophthalmoscopy under anaesthesia. As this method was considered as causing too much trauma to these sensitive infants, it was not used in this series. The examinations were carried out under homatropine mydriasis using indirect ophthalmoscopy. In this way, and despite the absence of anaesthesia, one was able to obtain a very good picture of the central parts of the fundus, as well as in the majority of the cases, a satisfactory view of the peripheral portions of the fundus. The American method of bending the scleral wall in over the area to be examined (REESE, HEATH), was not used because it would appear rather difficult to do without anaesthesia, when using indirect ophthalmoscopy, besides which the author feels that it might have an unfavourable action on a retina with tendency to separation of the different layers. In order to ensure good observation the upper eyelid was lifted up with a Desmarres' retractor and held in position by an assistant, whilst the examiner held down the lower lid with his finger. In cases where a greater enlargement was desired in order to make a closer examination of certain details, the examination was carried out by direct ophthalmoscopy. As a rule the fundi were examined once a week as long as the infants were in hospital, whereas only those cases

which did not show a normal fundus picture on being discharged from hospital were followed.

Of the 66 cases 10 weighed 1 500 g or less, 22 between 1 500 and 2 000 g, 28 between 2 000 and 2 300 g, and 6 weighed between 2 300 and 2 600 g. Six infants weighing under 1 800, died so soon after birth that they were only cursorily examined.

If one examines the smallest infants relatively soon after birth, either one cannot see the fundus at all, or, if one can see it, it is only with the greatest difficulty. This is due to the persistence of a remnant pupillary membrane as well as a remnant of the arteria hyaloidea with on occasions profuse branchings into the corpus vitreum. In addition to this the intensity of the light used for illumination is important. When the material was examined by the plane mirror persistence of pupillary membrane vessel remnants were seen in 11 of the cases, all of whom had a birth weight of less than 2 000 g, whilst in some of the other cases having a low birth weight one did not observe any such remnants, e. g. 2 infants weighing about 1 500 g, and 5 weighing between 1 600 and 1 700 g. Persistent pupillary membrane vessels disappeared relatively quickly, so that in the majority of the cases between 2 and 3 weeks old no remnants could be observed when examined by the plane mirror. If the examination had been carried out with a corneal microscope, the frequency of these changes would probably have been greater, and the duration longer. A persistent hyaloid artery was encountered in 13 cases, and which practically disappeared completely in all cases. In one of the cases, however, small remnants remained on the optic papillae which is a not uncommon finding in older persons. According to IDA MANN, TERRY, REESE and PAYNE, all the vessels in the corpus vitreum disappear with the exception of the main branch of the hyaloid artery, during the 8th—9th month of foetal life. Slight pupillary membrane remnants may persist and in some cases gross ones, are not uncommon in older persons.

When one examines the fundi of these infants there are three things which attract ones attention; i. e. 1) the grey colour of the papillae, 2) the frequent occurrence of abnormalities in the

calibre of the retinal vessels, 3) oedematous changes in the periphery of the fundi.

As far as the *colour of the papilla* is concerned, this was more or less grey at birth in most cases. In the material examined it was markedly grey in 20 cases, normal in 11 cases, and in the remainder it was grey but this was not so marked to be able to say with any degree of certainty that there was any deviation from the normal papillary colour. Most workers describing the appearances of the fundus in the newly born, emphasize that the papillae in full-term infants are frequently grey e. g. KÖNIGSTEIN, and STUMPF and VON SICHERER. The fact that they should be more grey or even grey in the greater number of premature infants than they are in full-term infants does not appear to have been the object for previous investigation. In the present material, however, there were 9 cases who, at birth, presented a normal papillary colour, or almost white papillae, and of these there were 4 who had a birth weight of less than 2 000 g, i. e. they weighed 1 500, 1 600, 1 600 and 1 810 g respectively. In some cases that had a low birth weight and very narrow retinal vessels, the papillae at birth were normal in colour or almost white, then they changed to grey before gradually regaining their normal colour. The stage at which the colour of the papillae becomes normal is not clearly shown in the available literature. In the material examined the papillary colour was usually more or less normal at the end of 4 or 5 weeks. For that matter it is hardly possible to tell when the actual change takes place in borderline cases, because it depends so much on personal experience, and several independent observers may disagree when they examine these cases. In every one of the cases examined the colour of the papilla was described as being normal before discharge.

Fundal haemorrhages were present in 4 cases. With regard to the incidence of this manifestation one should refer to CHASE, MERRIT and BELLOWS.

With regard to the *calibre of the vessels*, it has been possible to observe extremely narrow vessels as well as definite and on occasion pronounced dilatations. The narrow vessels were observed in those cases that had the lowest birth weight as soon as one was

able to make a detailed examination of the fundus, i. e. after the pupillary membrane and the anterior part of the hyaloid artery had disappeared. Extremely narrow vessels, as fine as a thread, were observed in 8 cases that had a birth weight of 1 900, 1 600, 1 600, 1 500, 1 500, 1 440, 1 270 and 1 170 g respectively. Of these, one of the 1 500 g infants died relatively early whilst in the other cases the calibre of the vessels became normal after about 14 days. Very narrow vessels have previously been observed by REESE, LA MOTTE and TYNER, and even by SCHLEICH in 5 cases as long ago as 1884. SCHLEICH did not say whether his cases were full-term or premature. Neither OWENS and OWENS nor HEATH mention anything about narrowing of the vessels in premature infants.

A marked increase in the calibre of the vessels, and especially in the veins, was observed in 10 cases, whilst this was not so marked in the others. As a rule this dilatation of the vessels was observed, only in those cases that either simultaneously or somewhat later manifested oedematous changes in the periphery of the fundus, and this will be considered more fully. Dilated vessels in the periphery of the fundus in connection with retinal duplications in the new-born have already been described by SEEFELDER, and this is, as already mentioned an early sign in retrolental fibroplasia.

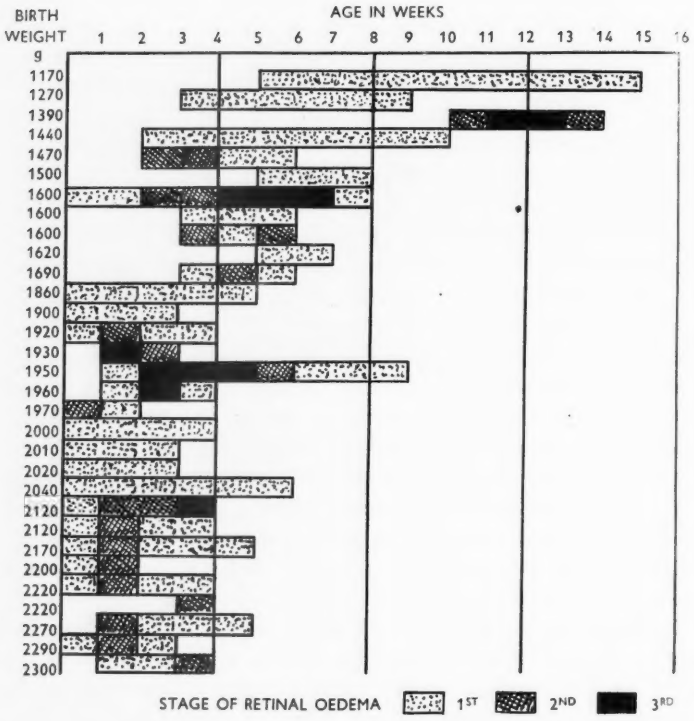
In about 2/3rds of the cases examined in this material, a more or less yellowish reflex was obtained from the *periphery of the fundus* but the degree of the change has been rather variable. In some of the cases, it has been possible to see that this yellowish, greyish-white, and at times pure white reflex has been conditioned by oedematous changes in the periphery of the fundus, whilst, in other cases, it has not been quite clear as to what might have been the cause. Oedematous changes should not be essential in order to obtain a yellowish reflex from the periphery of the fundus, but there are a number of factors in the actual method of examination which are of importance. For instance during the examination it has been seen that one could sometimes get a clearer picture with a red reflex if, (1) the distance between the examined eye, the condensing lens and the examiner's eye changed mutually, (2) the direction of observation was changed, and (3) a stronger positive

lens, +3, +4 or +5 was used in the ophthtalmoscope instead of a +2. It should be possible to explain these conditions as being due to the fact that the examined eye is so small and because of this the refraction is so markedly hypermetropic especially when examining the periphery of the fundus. In addition to this the choice of the source of illumination plays a part e. g. if one has a very powerful source of illumination the differences in colour are less readily appreciated. If one takes these conditions into consideration there still remains about 66 % of cases where one is unable to obtain a normal colour in the periphery of the fundus.

Having regard to the appearance of the peripheral changes, the material has been classified into 3 separate groups as follows: (1) a yellow-white reflex peripherally, but a fundus picture which does not differ essentially from normal, (2) a definite greyish-white oedema peripherally, and (3) a detachment of the retina peripherally, in which dark vessels protrude on a greyish-white retina and this sometimes shows newly formed vessels. In 48 cases one saw changes, which were usually bilateral and in 30 of these belonged to group 1, in 13 to group 2, and in 5 to group 3. If one is to examine these cases critically one is only able to say that the 18 cases in groups 2+3 could be regarded as having definite abnormal deviations, whereas among the 30 cases in group 1, one found all transitions from an insignificant yellow reflex to those changes as reckoned in group 2.

If one considers the birth weights of the 18 cases that had the most pronounecd changes, one will find no correlation between the birth weight and the nature of the changes. Of these 18 cases, only 6 weighed 1600 g or less, whereas the remaining 12 weighed between 1970 and 2270 g. In addition to this, in many of the cases which had the lowest birth weights, one was able to see a normal picture of the fundus as soon as examination was possible, and a normal red reflex was obtained during the subsequent period of observation. It is also striking that most of the cases that had extremely narrow vessels either at birth or immediately afterwards, suddenly developed dilated vessels and oedema peripherally (4 out of 8 cases that had vessels which were as narrow as threads, one of the remaining 4 cases died a few days after birth). A

Table 1.



similar occurrence is also reported by LA MOTTE and TYNER in 2 cases.

In most of the cases one was able to observe the development of the changes from day to day, in which the yellowish reflex changed to a greyish-white and later returned to normal. In Table 1, one considers the first appearance of the changes, and its duration in relation to the birth weight. In this table, only those cases which have shown definite changes, and which could be observed for a sufficiently long time have been included.

As previously pointed out, the table does not show any definite correlation between the frequency of these changes and the birth

weight, nor any correlation between the latter and the degree of the change. The only thing which can be said is that changes seem to occur later in children that have a low birth weight. The material, however, is too small to allow one to draw any definite conclusions in this respect, especially in the group with birth weights of less than 1500 g. Another source of error is the fact that infants with the lowest birth weights are kept under control for a longer time than those with higher birth weights. Some of these cases were only examined for a few weeks after birth, and thus one cannot say that they did not develop fundus changes later. In the majority of cases, however, this would then have meant a "relapse", as most of the cases had shown the less significant early changes, whilst in hospital, and these were followed until they had disappeared. However one must consider that relapses of this nature have not been encountered in the other cases, and for this reason it is probable that one has overestimated this source of error.

The greater tendency that seems to exist for the occurrence of changes later in the cases having a lower birth weight is of interest when one considers the aetiology. When one reads published reports about retrolental fibroplasia one finds difficulty in obtaining information about the earliest time at which retrolental fibroplasia can be diagnosed. However, it appears that retrolental fibroplasia in full-term infants can be diagnosed from birth, or shortly afterwards, whereas in premature infants it is not diagnosed usually until a long time after birth, especially in infants with a low birth weight. A tendency for fibroplasia to make an earlier appearance after birth, in a child with a heavier birth weight is met with in KRAUSE's material. INGALLS is of the opinion that this state of affairs might be of importance in the aetiology. In the 9 cases of OWENS and OWENS that had a birth weight of under 1300 g, the first changes were encountered when the infants were 3 months old, and similar conditions are present in the materials of GILGER and UNSWORTH.

HEATH points out that in the early stages of retrolental fibroplasia the *corpus vitreum* is usually hazy peripherally. Haziness of the corpus vitreum in the more advanced stages in retrolental

fibroplasia is reported by many authors. In the present material we have seen more pronounced haziness of the corpus vitreum in 5 cases, which has been most marked in the periphery, and all such cases showed insignificant changes in the periphery of the fundus.

Besides this one saw in four cases, a marked *dilatation of the vessels in the iris* which disappeared in a few days. This is very similar to the picture in rubeosis iridis diabetica.

Finally, some illustrative case reports:

Case 3. Birth weight 1 390 g. The eyes were examined for the first time at the age of 1 month when one saw grey papillae but otherwise normal eyes. One week later the retinal vessels were dilated, but the periphery of the fundus was not clear. At 11 weeks vessels were still dilated, but in addition to this there were greyish-white retinae which bulged forwards in the periphery of the fundi, and on these areas the retinal vessels appeared reddish-black in colour. 14 days later the oedema was even more marked, and was localized especially along the retinal vessels. After a further fourteen days the peripheral fields appeared normal, and in subsequent examinations for the next year the fundi remained normal.

Case 7. Birth weight 1 950 g. The infant was examined when two days old and the fundi showed grey papillae and a slight oedema of the fundi around the papillae. At two weeks there was a greyish-white reflex in the periphery of the fundus, but there was no definite oedema. A week later there was a greyish-white bulging of the retina with black-red vessels. Pronounced oedema especially along the vessels and a picture of a peripheral ablatio retinae remained for a further three weeks. In the right eye there was a wrinkled greyish-white retinal detachment in the fundus extending upwards, and this persisted until the infant was six weeks old, after which the fundus picture was normal. Later on, however, one could see a slatish-grey colouring peripherally, a condition which has been described by OWENS and OWENS in their cases of reversible retrolental fibroplasia.

Case 10. Birth weight 2 120 g. Examined first at 4 days and the fundi showed grey papillae with somewhat protruding vessels. In the fundus peripherally the reflex was greyish-white and the retina somewhat oedematous. A week later the veins showed a pronounced dilatation, and on the temporal side of the right eye there was a local grey-red retinal detachment. One week later the local detachment had disappeared, but the oedema in the periphery remained in both eyes. During the subsequent 14 days the condition remained unchanged, but suddenly the oedema

increased rapidly especially in the right eye so that there was the appearances of retinal detachment around the whole of the peripheral field. When the infant was examined at 6 weeks, the changes had almost entirely receded, and the fundus appeared to be normal.

Case 19. Birth weight 1 600 g. Patient was examined when 2 days old and the fundi showed a greyish-white reflex peripherally, but no oedema. The condition remained unchanged until the infant was 3 weeks old when the whole fundus peripherally appeared greyish-white. A week later the retinal vessels were markedly dilated and the peripheral vessels were dilated and tortuous but no definite oedema. After another week (i. e. at 5 weeks), local greyish-white retinal detachments with dilated vessels and newly formed anastomoses on the surface were visible. A week later the detachment was present around the whole of the periphery and remained so for about 14 days. Subsequently it decreased, so that when the infant was examined at 8 weeks for the last time, there was only a slight greyish-white reflex peripherally. Unfortunately the parents would not allow the child to be followed up after it had been discharged from hospital.

Case 20. Birth weight 2 120 g. At 1 day old there was an appeareance like rubeosis in the iris with markedly dilated vessels. The retinal vessels were markedly dilated, and there was a greyish oedema of the retina peripherally. Three weeks after birth the vascular dilatation had almost disappeared, and there remained only a grey reflex peripherally, but no definite oedema. This slight change persisted for a further week.

Discussion

The results obtained indicate that the changes previously reported as the first stages of retrolental fibroplasia, and which, according to OWENS and OWENS, might be reversible in certain cases are not specific for this disease and occur more frequently than has been previously thought. In addition it would seem that these are preceded by earlier changes consisting of markedly narrowed vessels in the retina, which are present from birth, as well as a pale fundus and a pale papilla, and are subsequently followed by a dilatation of the vessels of the retinae and this may be preceded by a yellow-white reflex peripherally followed by oedematous and ablatio retina-like changes. Simultaneously with this fundus change one observed in certain cases, a marked dilatation of the vessels in the iris which in appearance was reminiscent of rubeosis. In the present material it is worthy of note that one has been able to

diagnose these earlier changes in a vast number of cases and these changes were relatively independent of the birth weight, and were reversible in most of them, although in some it progressed to the typical picture of the early stages of retrolental fibroplasia. This perhaps gives a new aspect to this disease. In the author's opinion there is much to support the theory that these changes, including the peripheral retinal detachments represent simply normal development. However it is not clear why these changes are not always reversible, but have in certain cases, especially in American series progressed to a fully developed stage of retrolental fibroplasia in a very high percentage of cases. That a retrolental fibroplasia can develop even in full-term infants, and is then manifest either at birth, or immediately after is contrary to the idea that some special post natal influence is the cause. However one has to consider SZEWCZYK's preliminary report in which experiments have shown that the development of early stages of retrolental fibroplasia can be produced by lowering the oxygen content of inhaled air, and can be made to disappear by increasing the oxygen content.

Although one leans towards developmental aspects for this peripheral oedema, one feels that SZEWCZYK's anoxaemia theory for retrolental fibroplasia, might also explain the frequent occurrence of retinal changes in premature infants found in this material. The different times for their manifestation as well as the varying frequencies of early changes of retrolental fibroplasia in different hospitals may be due to different methods of treatment of premature infants with oxygen therapy etc.

Summary

In a material comprising 66 cases of premature infants, a regular examination of the fundi was carried out each week from birth. Amongst these cases there were 18 that presented a fundus picture similar to that described as being typical for early retrolental fibroplasia. These changes were reversible in all cases. Minor changes taking the form of a yellow-white colour and a slight oedema in the periphery of the fundus were observed in 2/3rds of the total material. If one considers the time at which these changes were first manifest in relation to birth, it would appear that the greater the birth weight the sooner changes become

apparent. When one considers the above and the high incidence of these minor fundal changes it is suggested that the changes described in this paper and in the early stages of retrolental fibroplasia are merely normal stages of development.

Aspect du fond d'œil chez les prématurés, avec observation particulière relative aux stades précoces de fibroplasie rétrolentale.

Le matériel examiné comprend 66 cas de prématurés, qui ont été soumis à un examen du fond d'œil dès le jour de leur naissance et chaque semaine depuis cette date. Parmi eux, 18 ont présenté une image du fond d'œil semblable à celle qui a été décrite comme typique de la fibroplasie rétrolentale précoce. Ces modifications ont été réversibles dans tous les cas. Des changements moindres, à savoir une couleur blanc-jaunâtre et un léger œdème à la periphérie du fond d'œil ont été observés dans les 2/3 des cas du matériel total. Si l'on note, en relation avec la date de la naissance, le moment où ces modifications ont été pour la première fois évidentes, il semblerait qu'elles surviennent d'autant plus tôt après la naissance que le poids de naissance est plus élevé. Compte tenu de ce fait, et de la fréquence relativement élevée des modifications mineures du fond d'œil, comme point de départ, l'hypothèse suivante est proposée: les modifications décrites, ainsi que les stades précoces de fibroplasie rétrolentale constituent les phases normales de développement, d'autant que les stades du développement complet de fibroplasie rétrolentale forment une progression continue, dont la cause est inconnue jusqu'ici.

Das Bild des Fundus oculi bei Frühgeborenen, mit spezieller Berücksichtigung der Frühstadien von retrolentaler Fibroplasie.

In einem 66 Fälle umfassenden Material von Frühgeborenen wurde jede Woche nach der Geburt eine regelmässige Untersuchung der Fundi durchgeführt. Unter diesen waren 18 Fälle, welche ein Fundusbild zeigten, welches dem für die Frühstadien der retrolentalen Fibroplasie beschriebenen ähnlich ist. Diese Veränderungen waren in allen Fällen reversibel. Geringere Veränderungen in Form einer gelblich-weissen Verfärbung und eines leichten Ödems des Fundus wurden in 2/3 des Gesamtmaterials beobachtet. Wenn man den Zeitpunkt des Manifestwerdens dieser Veränderungen in Beziehung setzt zum Geburtstermin, scheint es als ob jene um so früher nach der Geburt auftreten, je höher das Geburtsgewicht ist. Diese Gegebenheiten und die relative Häufigkeit der leichteren Fundusveränderungen bilden den Ausgangspunkt für die vorgetragene Hypothese. Die beschriebenen Veränderungen sollen zusammen mit den Frühstadien von retrolentaler Fibroplasie normale Entwicklungsphasen

darstellen, sodass die vollständig entwickelten Stadien von retrolentaler Fibroplasie nur in einer kontinuierlichen Fortentwicklung bestehen, deren Ursache bisher unbekannt ist.

Aspecto del fondo ocular en los prematuros, con especial referencia de los estadios primarios de la fibroplasia retrolental.

En un lote comprendiendo 66 casos de niños prematuros se hizo un examen seriado del fondo de ojo semanal desde el nacimiento. Entre estos casos 18 presentaron un fondo de ojo similar al que se describe como típico en los estadíos primarios de la fibroplasia retrolental. Estas alteraciones fueron reversibles en todos los casos. Alteraciones menos marcadas en forma de coloración amarillo-blancuzca y debil edema en la periferia del fondo ocular se observó en 2/3 del total de los casos. Cuando se considera el tiempo en el cual estas alteraciones se manifiestan en relación con el nacimiento parecería que en el elevado peso del nacimiento aparecen alteraciones precozmente. Si observamos la elevada incidencia de estas pequeñas alteraciones del fondo ocular se sugiere que las alteraciones descritas en este trabajo y en los estadíos primarios de la fibroplasia retrolental son meramente estadíos normales de desarrollo.

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CASE REPORTS

Lupus Erythematosus Disseminatus Treated with ACTH

by

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Case History

A girl, born August 29th, 1939 (No. 644/49 and 1016/50), was admitted to the Pediatric Clinic on June 13th, 1949.

Without known preceding infection she fell ill, in the spring of 1948, with transient joint symptoms in fingers and knees. There was no pyrexia and the E. S. R. was 108 mm. The symptoms abated and the E. S. R. dropped to 45 mm after 6 weeks in bed.

In December 1948, she developed an uncharacteristic form of facial erythema that was markedly sensitive to sunlight. Joint disorders lasting about 3 months set in once again in the following spring. As before, the E. S. R. was excessively high and this time the patient was slightly febrile initially. As the E. S. R. remained high despite prolonged bed rest, she was sent to the Pediatric Clinic in June, 1949.

On arrival she had no subjective symptoms and was afebrile. An uncharacteristic eruption was present in the form of red patches on the cheeks, around the eyes and on the legs. Apart from a soft systolic murmur, maximum over the apex, the patient's clinical state was normal. The E. S. R. (micro-method) was 41 mm; there were 5000 white blood corpuscles per cmm, and the antistreptolysin titre was 500 units per ml. The urine was normal. Neither ECG tracings nor cardiac radiography revealed any abnormalities. She displayed no signs of focal infection. It was considered that the patient had rheumatic fever, and penicillin therapy was instituted but had to be discontinued after some time owing to hypersensitivity reactions with aggravation of the facial erythema. It spread progressively and assumed a symmetrical butterfly pattern over the ridge of the nose until the picture ultimately was that of lupus erythematosus. She was sent home after 3 months in hospital. The erythema was then fairly faint. The E. S. R. was still raised — 50 mm — and moderate anemia was present. It was remarkable that the serum protein level, which was

normal on admission, had altered towards hyperglobulinemia on discharge: the total proteins showed an albumin-globulin ratio of 0.8.

She was readmitted to the Pediatric Clinic in October 25th, 1950, with increasingly severe polyarthritic symptoms which had set in several months earlier. The facial lesions had become worse before readmission, at which time there were no signs of debility. Typical erythematous plaques were seen on both cheeks and on the forehead. The skin was extremely dry. The pharynx was normal. There was no lymphadenoid enlargement. As before a soft systolic murmur was heard over the heart. The liver and spleen were not palpable. The retinae showed nothing out of the ordinary. Apart from slight redness and swelling of some interphalangeal joints on a few fingers the patient had no objective joint changes. E. S. R. 53 mm, Hb 13.2 g%, red cell count 4.6 million, white cell count 5 200, serum albumin 3.3%, serum globulin 4.9%, A : G ratio 0.7. An electrophoretic analysis performed shortly afterwards showed that the globulin increase chiefly concerned the alpha and gamma fractions. The girl's urine was altogether normal.

The symptoms remained on the whole unchanged for some time. The temperature was subfebrile, the facial skin changes varied somewhat, and both large and small joints were frequently painful. In addition to fairly marked normochromic anemia there gradually developed moderate thrombocytopenia. In conjunction with an ACTH test on November 20th, albuminuria and rather severe hematuria were observed for the first time. Granular and hyaline urinary casts began to appear some days later. Urinary abnormalities have remained unchanged since then.

ACTH therapy was commenced on November 21st, 1950. In a first course the hormone was in such short supply that no more than 12 mg could be given daily for 6 days. The general state improved somewhat and the facial erythema turned paler, but the E. S. R. remained unchanged and, if anything, the temperature rose. The administered dose was surely inadequate, but the preparation was extremely scarce at the time.

A second course of ACTH was administered between the 20th and 31st of December, 1950, 6 mg being given 4 times daily. By the second day after the beginning of the treatment marked improvement in the general condition, spirits and appetite had set in. The facial eruptions became still paler and looked like a slight blush. Having remained constant at about 38° for the past month, the temperature dropped to normal levels on the third day, but on the 11th day it again began to increase only to become higher at the end of the treatment than before it. The patient suffered no joint distress during the period immediately preceding the treatment, but a few days after its termination the symptoms reappeared. The albuminuria was markedly less severe throughout the period of treatment. While ACTH was being administered the E. S. R.

successively dropped from 68 to 46 mm, but it again went up after the treatment. Otherwise there was no definite change in the hemoglobin concentration or in the erythrocyte and leukocyte counts, nor was there any definite change in the serum protein composition.

Immediately after the end of treatment the patient's condition, as noted, again deteriorated; if anything she became worse than before ACTH was given. The subjective joint changes and the fever were more pronounced rather than better after treatment, but even two months after it the skin disorders had not flared up again. On January 10th, 1951, i. e. 10 days after the end of treatment, it was noted that the systolic murmur over the heart had altered character and become fairly rough and regurgitatory over a limited apical area. The ECG, which previously had been normal, now exhibited a deep Q wave and an inverted T wave in lead III and also elevated ST segments in leads II and III; these alterations since then have varied somewhat indicating myocardial damage. Radiography of the heart revealed slight enlargement of the left ventricle. At approximately the same time the liver was found to be somewhat enlarged. Signs of pleural effusions or ascites could not be demonstrated.

Discussion

This case was initially thought to be one of rheumatic fever, but when typical skin changes had developed and leukopenia as well as hyperglobulinemia were also present a diagnosis of lupus erythematosus disseminatus was considered definitive. This diagnosis was borne out by the continued course with prolonged fever and kidney and heart complications.

Several reports have been published of ACTH treatment in lupus erythematosus disseminatus. In this case the result of the treatment agreed well with that given in the literature, though here the dosage was very much on the small side and the treatment brief. The adult dose is as a rule about 100 mg daily for 2 or 3 weeks, and then it is decreased gradually to a maintenance dose large enough to prevent exacerbation of the disease. The duration of such a course of treatment varies widely but in the majority of cases 6—8 weeks is the rule.

A few days after the beginning of treatment it is usual to see a marked improvement in the general condition, often with initial euphoria and quite rapid disappearance of joint disorders, pain and exudations. The skin changes get paler after 5 to 10 days and have in some cases even vanished completely. As a rule the patient is afebrile after a day or two. The pyrexia has not responded to treatment in a few cases, and apparently it tends to return a few days after the cessation of therapy. Although normal values are not attained the E. S. R. commonly becomes lower. According to THORN et al. a lowered E. S. R. after an initial increase

usually indicates that the disease responds favourably to ACTH. THORN stated further that the preparation in 6 instances had induced definite reticulocytosis and slight leukocytosis accompanied by raised Hb and hematocrit values. Other authors have reported that higher erythrocyte or leukocyte counts cannot be domonstrated. A reduction in the alpha and gamma globulins and an increase in the albumin fraction following treatment has been noted in the majority of reported cases. This change sets in rather slowly and probably becomes noticeable only after prolonged treatment. ACTH apparently affects the renal changes in exceptional cases only. FERRIMAN and WILSDON described a case in which the albuminuria disappeared completely, and in one of THORN'S cases neither albuminuria nor hematuria had returned though 3 months had elapsed after the end of treatment.

Whenever remission occurred the treatment had been going on for a long time, but often it is doubtful whether a remission is spontaneous or a result of the treatment. Remissions lasting up to 6 months have been described. Many cases have been refractory to ACTH; ELKINTON suggests it may be due to some anti-substance. This treatment is obviously attended by considerable risks, and complications may set in after only a week or so. Common complications are hypertension and other symptoms of Cushing's syndrome, edema with its risks of sequelae in the form of heart failure, cramps, and psychotic manifestations. As the complications as a rule vanish when the drug is stopped, some authors are in favour of short, repeated courses of treatment. How ACTH attacks the disease is very imperfectly understood. BAEHR and SOFFER have proposed that abnormal enzymatic processes in the mesenchyme are inhibited.

In conclusion it may be said that adequate doses of ACTH may induce a clinical improvement in cases of lupus erythematosus disseminatus. In some cases there may be a longer or shorter remission. However, the disease is by no means cured by ACTH, even if it is the most effective known preparation in this puzzling disease.

Summary

The author describes a case of lupus erythematosus disseminatus in a girl aged 11 years. ACTH in doses of 24 mg daily for 12 days produced marked improvement which, however, lasted only as long as the course of treatment was in progress.

Lupus erythémateux disséminé traité par l'A.C.T.H.

L'auteur discute un cas de lupus érythémateux disséminé chez une enfant de 11 ans. L'A.C.T.H. donné à la dose quotidienne de 24 mg pendant 12 jours produisit une amélioration qui dura seulement pendant le temps du traitement.

Lupus erythematosus disseminatus, behandelt mit ACTH.

Der Verfasser beschreibt einen Fall von Lupus erythematosus disseminatus bei einem 11-jährigen Mädchen. ACTH in Dosen von 24 mg täglich während 12 Tage bewirkte eine ausgesprochene Besserung, die indes nur während der Behandlungsdauer anhielt.

Lupus eritematoso diseminado tratado con ACTH.

El autor describe un caso de lupus eritematoso diseminado en una niña de 11 años de edad en la cual la administración de dosis de 24 mg diarios de ACTH durante 12 días produjo una notable mejoría la cual persistió, sin embargo tan solo mientras fué realizado el tratamiento.

Addendum

Since the paper above was written the patient was treated with ACTH for two further periods with a dosage of 15 and 24 mg daily respectively, but no definite beneficial effect was noticed. The condition became gradually worse, the joints became swollen periodically, the hair started to fall out and decubital ulcers appeared on the legs. X-ray revealed a small amount of fluid in the abdominal cavity. The urinary findings did not change during the entire observation time. She died the 2nd Sept., 1951. At autopsy (by Dr. Ranström) the following were found. The heart was slightly enlarged. In the myocardium there were many fibrous scars and an extensive, diffuse fibrosis, indicating a previous rheumatic myocarditis, but no active inflammation was found. In the lungs there were scattered sub-miliary bronchopneumonic areas with infiltration of lymphocytes and epithelioid cells. The liver and the spleen had similar granulomas with central necrosis. The microscopic examination of the kidneys revealed hyaline cylinders in some of the tubules but the glomerulae were normal, which is remarkable. The examination of the pancreas revealed an acute pancreatitis which presumably had no direct connection with the basic disease. In the lymph nodes there was only a slight reticulosis, but no specific pathologic findings were noticed.

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Cortisone Treatment of Skin Involvement, Acrodermatitis Enteropathica, in a Case of Cystic Fibrosis of the Pancreas

by

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Acrodermatitis enteropathica is the name given by DANBOLT and CLOSS in 1942 to a disease presenting the following symptoms: A symmetrically diffused exanthema, localised especially around the natural openings, as well as the elbows, fingers, knees and feet, purulent paronychia with dystrophy of the nails, total alopecia, blepharitis with photophobia, and periodical attacks of profuse diarrhea with increased quantities of fat in the stools. The exanthema is most pronounced during the diarrhea periods, and in these periods there occurs a typical change in the patient's temperament, so that otherwise intelligent and good-tempered children become peevish and fractious and difficult to deal with. The malady is of a familial nature. In most cases it appears towards the end of the first year of life, often coinciding with the period of weaning. The disease is always fatal, after a chronic course with remissions and recurrences. Most of the patients die in early childhood and the longest

duration hitherto reported was up to the age af 11 1/2 years. DANBOLT and CLOSS believed the disease to be due to a pathological condition in the gastro-intestinal tract, but the underlying cause is unknown. All forms of treatment have proved to be ineffective. The disease has previously been described by the Swedish writers BRANDT and SÖDERLING and by the Danish author HAXTHAUSEN as being an atypical form of Hallopeau's acrodermatitis continua and by the American WENDE as a special form of epidermolysis bullosa hereditaria dystrophica.

Case report

Girl, born Febr. 22d, 1949. The parents were first cousins. A brother of the father died from an unknown cause when 2 months old. The child was the third in a family of three. The second child died at the age of 9 months, also from an unknown cause. Our patient was born at term after a normal pregnancy and labour. Birthweight 4 kg. Was never breast-fed. When she was nearly 1 1/2 years old, the stools began to become copious and somewhat lighter in colour than usual. From about the 1/8 1950 the child was languid and peevish and had little appetite. At the same time she began to have swellings in the legs. On the 5/9 50 she was admitted to the pediatric department of the Rikshospital. There was then noted deficient turgor and tonus. Weight: 8,700 g, while the normal weight for her height would be 9,000 g and for her age 11,500 g. There was erythema on the back of the thighs and in the rima internates. Injection of the mucous membrane of the vulva; rhagades in the lateral angle of the left eye; a distinct gingivitis. The tongue was somewhat redder than usual with granulation in the anterior part. The growth of hair on the head, the eyebrows and eyelashes was scanty. The abdomen was large and distended. Laboratory examinations: Hb. 73 per cent. Serum proteins considerably reduced. Albumin: 1.9 g. Globulin: 1.10 g. Alb./glob.: 1.72. Calcium and phosphorus distinctly reduced, to 7.9 and 3.1 mg per cent respectively. Phosphatase: 1.8 Bodansky units. Stools: light in colour and containing much fat. In dried feces there was 37 per cent of fat, of which fatty acids formed 63.8 per cent.

The blood sugar curve was flat. The bone marrow highly hypoplastic. The feces and duodenal juice contained trypsin, although less than usual. Radiography of the skeletal system revealed pronounced osteoporosis.

On ordinary diet she became much worse, with severe diarrea and loss of weight, in spite of a greatly increased edema. The gingivitis and rhagades increased and at the same time there developed a symmetrically diffused vesicular eruption on the face, a peculiar brown pigmentation of the skin on the face, scalp and arms, as well as aphthous sores on the mucous membrane of the mouth and blepharitis with pronounced photophobia. We were inclined to regard the disease as being a pancreatic

fibrosis, although the finding of trypsin and the absence of symptoms from the upper air-passages, with the normal radiological findings in the lungs, might be deemed to be more suggestive of celiac disease. The patient was given the usual diet for patients with celiac disease and in addition vitamines A, B, C, D by intramuscular injection. On account of the existing hypoproteinemia, infusion of plasma was also tried, but after this she grew much worse, with increasing edema; the Hb. fell to 52 per cent.

The eruption became steadily more pronounced and acquired more and more the aspect of ariboflavinosis. We therefore gave her 5 mg of lactoflavin intramuscularly every second to every third day from $^{23}/_{9}$ 1950. This resulted in a rapid and striking improvement. The skin cleared and the sores and the rhagades disappeared. The skin then began to scale and the pigmentations vanished to a large extent. The child's appetite, general condition and temperament grew much better and she began to sit up. The stools had an improved appearance, were most often better formed and less offensive than before. As a rule she had only one motion per day. A sample taken on the $^{17}/_{10}$ 1950 contained, however, in the dried mass 52 per cent of fat, of which 73.9 per cent was in the form of fatty acids. The serum protein increased somewhat, chiefly the globulins. During this period she also tolerated an ordinary light diet. After a catarrhal infection which was treated with procaine penicillin, her condition again became worse: the eruption reappeared and the edema increased, followed by attacks of vomiting and later diarrhea. She was again put on the same strict diet as before. The vomiting then ceased but the eruption increased, while the edema varied greatly. On $^{7}/_{11}$ 1950 she again got worse after a catarrhal infection: she had never any cough. Aureomycin was tried for 14 days, but without definite effect. From $^{4}/_{12}$—$^{27}/_{12}$ we tried pancreatin. She tolerated the drug quite well, but lost her appetite completely. The stools were possibly somewhat better during this time, with usually only one motion per day. The serum protein values were constantly low, always under 4 g per cent. The bone marrow remained hypoplastic and the prothrombin content had now fallen to 19 per cent. The Hb. remained at around 70 per cent, with an index of about 1.

On account of the greatly hypoplastic bone marrow we tried vitamin B_{12}, 40 micrograms every second day from $^{22}/_{1}$ to $^{31}/_{1}$ 1951, and obtained a maximum rise in reticulocytes on the 7th day with values of 38 per thousand. This was followed by a fall. Folic acid was also tried 3 to 5 mg every second day from $^{27}/_{2}$ to $^{8}/_{3}$ 1951, with the highest reticulocyte value of 24 per thousand on $^{7}/_{3}$. Meanwhile her general condition and skin eruption grew steadily worse. She now presented the typical picture of acrodermatitis enteropathica.

From 8th to 10th of March the patient was almost moribund. She was

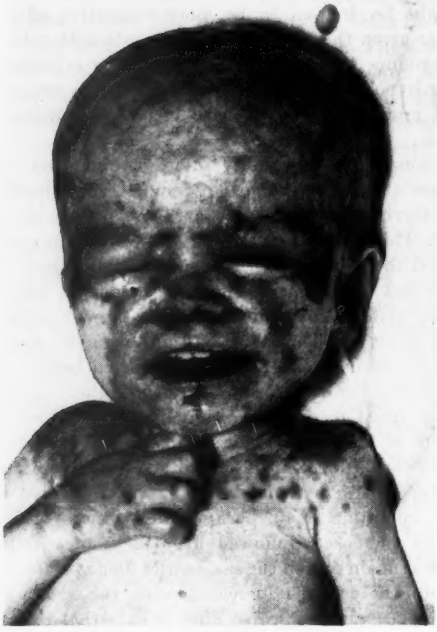

Fig. 1. Before treatment.

now given intramuscularly 25 mg of cortisone daily and a striking effect was noted within a few days. In the course of four days she became free from fever. She had a far better appetite and gained 1 kg in weight. Whereas in her bad periods she had been peevish, fractious and ill-tempered, she was now in good humour and after the lapse of four days she was mostly sitting up and swinging in her rocking-chair. The eruption disappeared entirely in the course of a short time, but the skin still remained thin, atrophic and of a peculiar greyish pallor, sometimes with a little pigmentation on the most severely affected parts. The photophobia vanished completely, the necrosis, that developed after the teeth that had fallen out, rapidly healed and, apart from one tooth which was quite loose when the cortisone therapy began, she did not lose a single tooth during that treatment. The paronychia subsided and new nails with smooth surfaces began to grow. The stools also improved with 1 or 2 motions per day. She was now given 25 mg cortisone

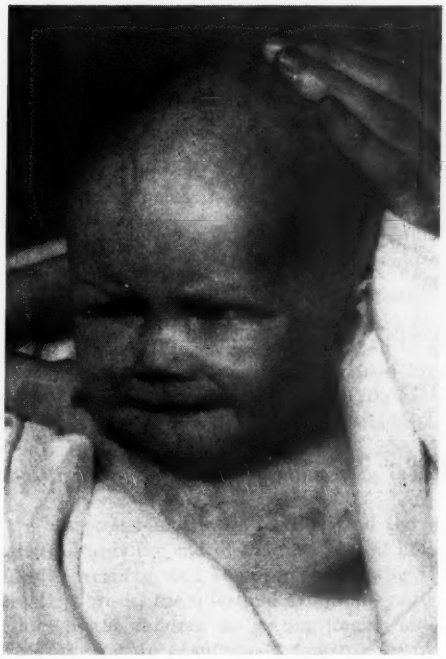

Fig. 2. After treatment.

daily until the 10th April, i. e., for 5 weeks; after this the dose was decreased to 12,5 mg for a further 4 days. Quite early on we ceased to give the patient human milk, which was in fact the only food she tolerated before the cortisone therapy began, and let her have a celiac diet with aminosol and plenty of dried milk. She had grown only 1 cm since her admission on $^5/_9$ 1950, and as X-ray examination of the skeletal system revealed a great degree of osteoporosis (but, strangely enough, only slightly retarded development of the ossification centres), we now gave her also calcium tablets and again tried vitamin D_2, 250,000 I. U. We also continued with the transfusions of blood. Her weight rose by 2 kg without any increase in the edema, from which she was never quite free, although it varied greatly from time to time. The photographs (figs. 1 and 2) will give a good idea of the improvement in the patient's condition. A similar impression will be obtained from the laboratory examinations, as well as from the blood sugar curves.

So far as the fat excretion is concerned it must be noted that at the end of the treatment the patient had a far freer diet than before and that she ate far more.

	$^{10}/_{3}$ 1951	$^{14}/_{4}$ 1951
Serum proteins	2.75 per cent	4.40 per cent
Albumin	1.45 » »	2.90 » »
Globulin	1.30 » »	1.50 » »
Alb./glob.	1.11	1.93
Serum calcium	6.8 mg per cent	8.2 mg per cent
Serum phosphorus	3.1 » » »	4.28 mg per cent
Prothrombin	19 per cent	84 per cent
Hb.	70 » »	70 » »
Red blood cells	3 420 000	3 660 000
Index	1.03	0.96
Reticulocytes	0.84 per cent	5.7 per cent
Total bases	150.5 mEq.	147.2 mEq.
Chlorides	98 mg per cent	110 mg per cent
Fat excreted in feces per 24 hours.....	12.9 g	2.12 g

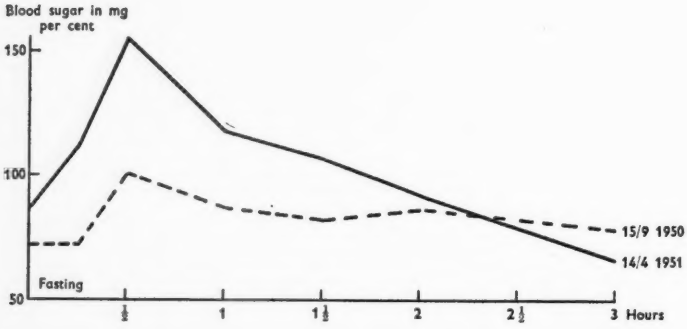

Fig. 3. After ingestion of 15 g glucose in 60 cc water.

Five days after conclusion of the cortisone treatment the patient unfortunately died following an intratibial transfusion of directly compatible blood of similar type from a donor who had previously on several occasions given blood to our patient. At autopsy there was found, besides fibrosis of the pancreas, multiple fat embolism of the lung, and this was probably the direct cause of death. The bone marrow had on numerous aspirations proved to be very rich in fat and decidedly hypoplastic

Comments

The patient presented the typical changes in the skin which are characteristic of acrodermatitis enteropathica, as well as total alopecia, blepharitis with photophobia, purulent paronychia with dystrophic nails, periodical attacks, more or less severe, of distinctly fatty diarrhea, with aggravation of the skin symptoms in the bad periods, during which there appeared a typical alteration in the patient's psychic state. In our case there also developed necrosis of the alveolar margin in the lower jaw with a falling out of all teeth; none of these were carious.

The cause of the disease has hitherto been unknown. In our patient fibrosis of the pancreas was found to exist and the question arises whether that disease always constitutes the underlying cause of acrodermatitis enteropathica and whether this syndrome must then be included in the symptomatology of pancreatic fibrosis. In the cases hitherto reported the possibility that they may all have been due to fibrosis of the pancreas cannot be precluded. The differential diagnosis from celiac disease is difficult and it is possible that the symptoms may also appear in other diseases characterized by defective resorption from the gastrointestinal tract.

The disease has been found to be familial, and the symptoms have usually appeared towards the end of the first year of life, almost always in connection with weaning, and thus somewhat later than is usual in cases of pancreatic fibrosis; the intestinal symptoms need not always be prominent so long as the children are getting human milk, as the lipase therein can split the fat to a sufficient degree. Moreover, it may be assumed that the external secretion from the pancreas does not cease entirely. We, and other investigators, have found greatly increased quantities of fat in the feces, mostly in the form of free fatty acid. This is a frequent finding in cases of pancreatic fibrosis, since the lipase in the intestine splits the neutral fat. Catarrhal infections with aggravation of the symptoms may occur, but, contrary to what is usual in fibrosis of the pancreas, there is little coughing, and X-ray examination of the lungs reveals normal conditions. Such findings have also previously been reported (DANBOLT). The positive findings of trypsin in duodenal juice are not against a diagnosis of pancreatic fibrosis.

How are we to explain the poor effects of pancreatin treatment? The disease was so far advanced that it was no longer enough to provide a substitute for the external function of the pancreas, since there had by now developed defective absorption in the intestinal mucosa. It is then possible that many of the symptoms and changes — for instance, the eptihelial degeneration in the bronchial tree, which was formerly supposed to be due to lack of vitamin A — may be ascribable to this

secondary deficiency of absorption. It would therefore be of great interest to investigate the epithelium of the bronchial tree in patients who die of meconium ileus and to compare the findings with what is seen in patients who have been brought safely over the ileus but who succumb later on in the course of the illness.

That the functional derangement is not the same in celiac disease as in acrodermatitis is also shown by the difference in type of anemia and in the blood sugar curves. In fibrosis of the pancreas there is, as in our case, a mild degree of anemia, usually of hyperchromic or normochromic type. In celiac disease the anemia is usually more pronounced and markedly hypochromic, with low values for serum iron. In our case the serum iron values were normal. By far the greater part of the iron is absorbed form the duodenum and the upper portion of the jejunum and the fact that such low serum iron values are found in case of celiac disease speaks strongly for the assumption that the deficient absorption involves the whole of the intestinal tract. In case of pancreatic fibrosis the failure in absorption first comes into evidence somewhat lower down in the intestine. Herein we have probably a partial explanation of the different types of anemia.

In celiac disease the blood sugar curve is flat, with low initial values. In acrodermatitis enteropathica we find high initial values and a sharp and rapid rise (DANBOLT). In our case the curve was somewhat flat at first, afterwards normal.

There is seen on examination of the blood at an early stage of the disease little evidence of defective absorption and metabolic derangement. In celiac disease we find comparatively early on in the illness a slight reduction of serum calcium, with pronounced osteoporosis and greatly retarded development of the ossification centres — a finding which is met with far later in acrodermatitis enteropathica. The calcium metabolism must therefore be different in the two conditions, and in such manner that the absorption of calcium is most reduced in cases of celiac disease.

In our patient the cortisone treatment produced a striking effect both on the affection of the skin and on several other symptoms. The paronychia subsided and at the same time normal nails began to grow. The teeth ceased to fall out, the blepharitis and photophobia disappeared. There developed a marked improvement in the general condition, with better humour, good appetite and a definite gain in weight, while the patient was able to tolerate an ordinary diet much better than before. The stools had also for the most part improved. In the blood the improvement was reflected in an increase of the serum proteins, especially of the albumin fraction, and the alb./glob. ratio became normal. Likewise there was an increase in calcium, phosphorus, prothrombin and reticulocytes, while the somewhat low blood sugar curve became completely normal.

This raises the question of the pathogenetic importance of the adrenal glands in pancreatic fibrosis and in celiac disease, which has so much in common with fibrosis of the pancreas. In both these diseases it is the fat metabolism that is most affected, and by closer examination of this one might perhaps come somewhat nearer to an understanding of the cause of these diseases. It is assumed that the fatty acids produced by the action of lipase from neutral fats enter into an easily dissolvable combination with the bile acids and then become diffused within the mucosa of the intestine. Here the bile acids are again split off and the fatty acids are converted to phospholipoids (by phosphorylation), whereupon the neutral fat is resynthetized by being combined with glycerin. In cases of celiac there is, as already mentioned, believed to be a lack of absorptivity in the whole of the intestinal mucosa. This reduced phosphorylation is thought to be secondary to an insufficiency of the adrenal cortex, which, again, is due to absence of an intrinsic or extrinsic factor. VERZAR believed that the primary cause was a shortage of lactoflavin. The fact that the resorption curve for vitamin A and the blood sugar curve show improvement on use of liver extract and of the vitamin B complex is in favour of this deficiency hypothesis. This may be said to accord with the finding in our case that later on in the course of the pancreatic fibrosis there comes a secondary failure of the adrenal function with reduced phosphorylation in the intestinal mucosa, possibly due to a primary lack of riboflavin. For we noted a distinct improvement after injections of riboflavin; the skin symptoms regressed considerably and at the same time the child's temperament improved, she got better appetite, more normal stools and a marked increase in weight. After a subsequent relapse there was then seen the striking effect of cortisone.

What may we then suppose to be the action of cortisone in acrodermatitis enteropathica? What is it that takes place in the tissues? In case of skin diseases for which ACTH and Cortisone prove to be effective we find, before commencement of the treatment, increased quantities of hyaluronic acid and increased number of plasma cells in the corium. The plasma cells constitute the mother substance for hyaluronic acid and are also supposed to be the peripheral conveyor of the hormonal action to the tissues. During ACTH and Cortisone therapy the number of plasma cells and the content of hyaluronic acid decrease, only to rise again when the treatment is discontinued. This is thought to be due to the fact that the content of a substance which is found in the serum of all human organisms and which inhibits the production of hyaluronidase, is reduced, with consequent liberation of hyaluronidase; this in its turn acts upon the hyaluronic acid and splits it. In case of the skin this is easily verified by taking biopsies.

We should, it is true, be somewhat reserved in our enthusiasm for cortisone, since the drug has as a rule only a symptomatic effect. In a con-

dition such as celiac disease, however, with a course extending over many years, a symptomatic improvement will mean very much, especially by curtailing the bad periods and possibly bringing the patient permanently over these periods and thereby considerably shortening the duration of the illness. We cannot expect to be able to decide as to the value of the drug over a long time, since it is very difficult to judge its effects in an illness with such a varying course as celiac disease. We hoped that the good effect we found in our case with pancreatic fibrosis would also be attained in cases of celiac disease, and we have now begun to treat such cases partly with cortisone and partly with ACTH, in combination with injections of vitamin B. The preliminary results are promising. We shall later give an account of the results of these experiments.

Summary

A case is reported of a child with fibrosis of the pancreas presenting a picture which resembled that earlier described in the disease designated acrodermatitis enteropathica and the possibility is suggested that this latter disease is always due to pancreatic fibrosis. The previously reported cases seem to support this assumption. The patient was treated with cortisone with very good effect. A preliminary account of the use of cortisone therapy for celiac disease is also given. The results noted appear to be encouraging.

Traitement par la cortisone d'une affection cutanée, acrodermatite entéropathique dans un cas de fibrose kystique du pancréas.

L'auteur rapporte un cas de fibrose du pancréas, présentant un tableau tout-à-fait analogue à celui décrit antérieurement sous le nom d'acrodermatite entéropathique, et il suggère la possibilité que cette dernière maladie soit toujours dûe à une fibrose du pancréas. Les cas rapportés auparavant semblent confirmer cette supposition. Le malade a été traité par la cortisone avec un très bon effet, et l'auteur, en même temps, donne un exposé préliminaire concernant l'emploi de la même thérapeutique, également dans la maladie coeliaque. Les résultats obtenus jusqu'ici semblent très encourageants.

Cortisonbehandlung von Acrodermatitis enteropathica in einem Fall von cystischer Pankreasfibrose.

Der Autor schildert einen Fall von cystischer Pankreasfibrose mit einer Hauterscheinung, die dem Bilde, welches der früher beschriebenen, als Acrodermatitis enteropathica bezeichneten Krankheit, ganz gleicht. Die Möglichkeit, dass die letztere immer im Laufe einer Pankreasfibrose auftritt, wird erörtert. Die früher berichteten Fälle scheinen diese An-

nahme zu stützen. Der patient wurde mit gutem Erfolg mit Cortison behandelt. Eine versuchsweise eingeführte Cortisonbehandlung von Coeliakie hat bisher ermutigende Resultate gegeben.

Tratamiento con cortisona del proceso cutáneo de la acrodermatitis enteropatica en un caso de fibrosis quística del páncreas.

El autor presenta un caso de fibrosis quística pancreática cuyo cuadro clínico era en todo semejante al de la enfermedad designada como acrodermatitis enteropática y sugiere la posibilidad de que esta ultima enfermedad sea siempre debida a una fibrosis quística del páncreas. Los casos previamente descritos de esta afección apoyan esta presunción. El paciente fué tratado con cortisona con buenos resultados y el autor ha procedido al propio tiempo a hacer un estudio preliminar respecto al empleo de la terapéutica por cortisona en la enfermedad celíaca. Los resultados preliminares parecen ser esperanzadores.

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Proceedings of the Section for Pediatrics and School Hygiene of the Swedish Medical Society

Meeting, October 12, 1951

P. Nordenfelt: **An account of the Committee Report on Day Nurseries and Nursery Schools.**

Elsa Brita Nordlund: **The Doctor and Mother of a Backward Child.**

Meeting, November 24, 1951

Ingvar Alm: **Present medical and social-medical problems in infant homes.**

The author has studied the frequency of infections at the 8 infant homes at the disposal of the Stockholm branch of Social Welfare. During 1950, 416 children were admitted to the 179 available places. Infant homes with good quarantine and isolation facilities show the lowest disease figures, even though a fairly large number of cases with infections were admitted. As far as infections are concerned, homes situated in the periphery of the city may manage quite well with only moderate isolation facilities. Similar institutions in Stockholm show a greater incidence of infections, which are no doubt, staff-borne.

In a big city, the social structure of the clientele and the high frequency of infections render it essential for some infant homes to have well-appointed departments for admission and isolation. In addition, some peripherally situated institutions are required to admit children direct from the Maternity Hospitals or other places with a low infection frequency. Owing to their many small rooms, the first-mentioned infant homes require a comparatively big staff but, by centralising the staff for cooking, cleaning up etc., it should be possible to run them with a staff of the present size. Such time as may be saved should be utilised to improve the mental care of the children.

B. Söderling: **Social causes of psychosomatic troubles in the everyday practice of pediatricians.**

The fundamental social tone and atmosphere about a growing child is often loaded with antiquated conceptions and is steeped in prejudices. Here we have to consider, inter alia, our high school teaching and religious

education which produce a not inconsiderable crowd of mentally deficient individuals in the society. The demands of propriety, the general breaking-in mentality, with punishments and disciplinary methods, the dispensation of social justice, the difficulties of children of divorced parents, the woman's failure to understand the care of children that would help her to understand the child's world, etc. All this goes to prove that the regard for the human values in children still remains unsatisfactory. The often unbelievable ignorance of mothers in the care of a child and a home, together with their own insecurity, creates feelings of unsafeness and anguish in the infant. Children of alcoholics suffer a severe mental neglect and are exposed to mental trauma. Serious deficiency symptoms, extreme shyness, listlessness and anguish characterize a psychosomatic syndrome. Society lacks resources, sufficient to help a mother.

The above observations exemplify a few factors of mental hygiene affecting children in their environment and illustrate a definite aspect of the practice of pediatricians. It seems a proper and a fairly necessary, and indeed a gratifying, task for a pediatrician to take an active interest in such matters as affect the fundamentals of society. We are too often confronted with disconnected symptoms and special diagnoses.

Elsa Brita Nordlund: **A report from the White House Conference 1950 (A healthy personality for every child).**

B. Broman: **Coomb's reaction, its clinical significance.**

K.-A. Melin and K.-M. Herrlin: **On the treatment of spastic children with parpanit and artane.**

Parpanit and artane have both been described as useful in cases of Parkinsonism, particularly with regard to the characteristic rigidity. Parpanit has been applied in 9 cases without any objective improvement. On the other hand, artane, a synthetic piperidine derivative, produced by Lederle, with a parasympathico- and spasmolytic effect, has in 5 tests been found beneficial with regard to relieving increased tone, and in one case a pronounced athetosis. The artane dosages have been gradually increased from 0.5 mg to 0.5 mg × 6 or 1 mg × 4. In two cases the treatment has been continued for many months. No noteworthy side effects have been observed.

P. Karlberg and S. Iggbom: **On BMB-determinations in older children.**

John Lind and Carl Wegelius: **Changes in the circulation at birth.**

Changes in the circulation in newborns have been studied by angiocardiography. Immediately after birth, a contrast medium was injected

into the umbilical veins of 6 full-term infants. All of them had cried before the injection. The injections met with marked resistance. Apart from a local contraction of the vein, the angiocardiograms showed a pronounced contraction of the sinus venosus. In one case, rhythmic contractions of the venous duct were ascertained. By venous angiocardiography the ductus arteriosus was found patent, in some other instances, to have closed a few hours after birth. In two cases, a retrograde aortography was performed 2—6 hours after birth. It was not possible by this method to pass any contrast through the ductus arteriosus. In a 22 weeks old fœtus, retrograde aortography disclosed rhythmic contractions of the ductus. The venous angiocardiograms did not reveal any patent foramen ovale. These observations confirm that an immediate and functional closure had taken place. Angiocardiographic findings in connection with asphyxia in newborns have shown that the foramen ovale has either failed to close or has reopened. In 4 cases, it was wide-open. Angiocardiography has shown that the blood flowing directly to the left atrium comes chiefly from the inferior vena cava. This conforms to the course of the circulation in human foetuses that has been ascertained earlier by the above-mentioned authors. In 2 cases, the ductus arteriosus was found to be open with a direction of the foetal flow from the pulmonary artery to the aorta.

The authors therefore suggest that, in cases of asphyxia, blood saturated with oxygen should be applied to the medulla via the inferior vena cava. This may explain the beneficial effect of gastro-intestinal therapy according to YLPPÖ-ÅKERRÉN. In shock treatment, an injection of oxygenated blood into the umbilical vein is suggested, since the oxygenation is then combined with the anti-shock effect of a blood transfusion. This method has been tried in human foetuses, and it has been possible in these cases to note an improvement in colour, a return to normal of a simultaneously registered electrocardiogram and, not unlikely, prolonged survival (as recorded by an ECG curve).

E. Mannheimer, E. Bengtson and J. Winberg: **Congenital isolated mitral defects.**

Accounts are given of a girl, 1 $^1/_2$ year old, with a congenital isolated mitral stenosis, and a girl, 13 years old, with congenital mitral stenosis and insufficiency. Diagnosis has been ascertained in these cases by catheterization of the heart, electrocardiography, including oesophageal leads, phonocardiography and angiocardiography. The girl of 1 $^1/_2$ year was operated upon. The patient died during the operation. Nevertheless, operative treatment is not regarded as hopeless in such desparate cases. In both these cases, the aetiology was noted as foetal endocarditis.

O. Melander and G. Öberg: **Antibody formation and feeding. Some experiences from animal experiments.**

The significance of protein in a diet for the formation of antibodies has been investigated on lamb twins. One was suckled, the other fed with a mixture of cow's milk. The animals were inoculated with an influenza virus. Titration of antibodies was performed as described by HIRST. The normally fed lambs have, generally speaking, disclosed considerably higher antibody titres than the artificially fed ones. The resorption of high-molecular peptides from the intestine and its significance for the building-up of immune globulins are discussed.

H. Eriksson, L. Hesselvik and B. Vahlquist: **On combined triple routine immunization in infants.**

A brief report is given of the advantages of routine immunization with combined diphtheria-tetanus-pertussis in young infants. Three injections were successively administered between 3 and 6 months of age. Immunity response, as well as side reactions, were studied. A detailed report will be published later.

P. Hedlund and R. Lagercrantz: **Studies of streptococci in Scarlet fever.**

Isolation and type determination of the hemolytic streptococci have been carried out in 1,700 cases of streptococcal diseases. The isolation and type determination of the hemolytic streptococci was possible in 85 per cent of about 1,400 cases of Scarlet fever. The types of streptococci most common in the scarlatina patients were also most often found in the case of other streptococcal diseases. The age distribution, however, differed. In scarlet fever the maximum frequency was between 4 and 12 years of age, while in tonsillitis, the frequency remained the same in higher ages. Though the tonsillitis material is to some extent selected, the results of the investigation confirm earlier experiences, viz., that the patients are susceptible to the Dick toxin chiefly in childhood, while individuals of a more advanced age will seldom react with eruption. As a rule, some particular type predominated for a long period among the scarlatina patients, as well as among other streptococcal diseases. In the scarlatina patients, a change of type was a comparatively rare occurrence, though it was significantly more often noted among the complicated, than among the uncomplicated cases. Still, the majority had complications without any change of type. After a recurrence, some cases revealed a change of type, while, in others, the same type reappeared.

Börje Holmgren: **Electro-encephalographic investigations of acute infective diseases.**

The frequency of pathologic electro-encephalograms in the acute stage of the following diseases (percentages): psychoneurosis (with conditions suggestive of encephalitis) 0, uncomplicated parotitis 3, uncomplicated cases of morbilli 15, poliomyelitis 30—40, parotitis-meningo-encephalitis 40, serous meningo-encephalitis 70, morbilli-encephalitis 90, purulent meningitis 90, tuberculous meningitis 100, and pertussis-encephalitis (8 cases with convulsions) 100.

In the meningo-encephalitis, pronounced slow dysrhythmia will be found, which is either diffuse or focal, consisting at the acute stage of high 2-4-waves per secoud. The dysrhythmia disappears in stages, being replaced by more rapid and regular types of waves. Throughout, a very slow and sparsely occurring basic rhythm will be noted in the acute stage, progressively becoming more rapid and clear, as the patient's condition improves and the cerebral dysrhythmia disappears. In a not inconsiderable number of cases, the dysrhythmia will remain for several months and, occasionally even for years. In most cases, this well conforms to the clinical findings. In two cases, the dysrhythmia was very suggestive of epilepsy, with a "wave-and-spike" complex as well as focal spikes, and these cases were recovering from encephalitis, indicating a latent post-encephalitic injury, sometimes connected with manifest symptoms of epilepsy. It is possible, in most instances, to diagnose an encephalitis by ECG. This method is particularly useful in doubtful cases when the lumbar puncture proves negative, and also in following the course of the cerebral dysfunction, in order to ascertain if or when it has disappeared, as well as in the differential diagnosis between an organic and a functional cerebral disturbance.

E. Carlens and B. Hellström: **On bronchial changes in primary tuberculosis in children.**

Bronchoscopy has been performed in 23 cases of primary tuberculosis in children, when clinical or roentgenological findings have suggested bronchial changes. In altogether 18 cases, changes were ascertained. 13 had intrabronchial processes in the form of granulations and cheesy necroses. The importance of bronchoscopy is stressed. It is a useful diagnostic method to recognise cases with intrabronchial changes, since, in those instances, we regard treatment with PAS and streptomycin as indicated. In addition, bronchoscopy renders draining of the bronchus possible, thus providing a better airing of an atelectatic portion of a lung, which may be important in the prophylaxis against bronchiectasis.

L. Hesselvik: **Morbidity in children from day nurseries during their first years at school.**

DISCUSSION. —

C. Gyllenswärd pointed out the source of error implied that, among children admitted to day nurseries, those susceptible to infections are rapidly sorted out, and that, consequently, the frequency of infections among home-bred children becomes overrepresented.

Gunnar Laurell and Hans Ronge: **The use of ultraviolet rays at children's hospitals.**

The investigations were performed at the premature department of Sachs' Hospital for Children. This department occupies 5 rooms, and altogether 20 beds, 4 in each room. Room I contains 4 wholly closed boxes with sliding-doors. Entrance to the department takes place through a lock. Ultraviolet lamps are installed in all the wards, corridors and locks in the doctor's office, in one suckling-room and a waiting-room outside it. Two types of lampfittings are used for the installations. In both instances, the ultraviolet fluorescent tube is placed in front of an aluminium reflector. By means of a system of lamellae in front of the reflector, the rays are directed, as desired. When the purpose is to irradiate the upper air space of a room, the rays should have a vertical direction. If a screen is wanted, they should be directed straight downwards.

The efficiency of an installation was tested by spraying out into the air various bacteria (prodigiosus, staphylococci and coliform bacteria), and determining their disappearance with and without irradiation. This was done with a so-called Bourdillon's slit sampler.

To sum up, the ultraviolet light has proved well adaptable to the daily work at a Children's Hospital, even when used day and night. Bacteriologic air investigations showed that the installation will fulfil all expectations. At present, investigations regarding the significance of ultraviolet rays in the prevention of nosocomial infections are being performed.

Meeting January 11, 1952

L.-M. Briandt: **Postvaccinal complication from the central nervous system.**

An account is given of a case of postvaccinal encephalomyelitis, concerning a girl, 8 years of age, who fell ill acutely, a fortnight after a smallpox vaccination, with fever, nausea and increasing drowsiness. Flaccid pareses and a symmetrical reduction in sensibility in both legs, c.s.f. changes and a pathologic EEG were noted. She recovered completely in 3 weeks.

Justus Ström: **Panhematopenia with a secondary hypersplenism.**

At the end of 1949, the parents of a boy, who at that time was 4 1/2 years old, noticed that he, in connection with a pertussis, developed a good many petechiae and hematomas on his body. This was, in rapid succession, followed by a septic lymphadenitis on his neck, a secondary infection of varicellae and, finally, a pharyngeal affection with sanguineous nasal catarrh. He was admitted at Stockholms Epidemisjukhus (the Hospital of Epidemic Diseases) as a case of diphtheria. Note was made of an anemia (Hb 8.3 g%, red corpuscles 3.7 mill.), a leukopenia (1000 white corpuscles) with only 8 per cent of myeloid elements and not a single segmented neutrophil cell, as well as a thrombopenia (about 30000 thrombocytes). From that time, he was again and again admitted at the hospital for treatment of various infections in the skin, pharynx and air passages. To begin with blood transfusions gave temporary relief. On three occasions hemolytic crises occurred. There were no indications of congenital hemolytic anemia or of acquired hemolysis, on account of auto-antibodies (Coomb's test negative). In November 1950, enlargement of the spleen was noted. During his latest hemolytic crisis, in March 1951, splenectomy was performed on vital indication. The spleen showed an abundance of iron pigment, as well as an extremely pronounced hyperplasia of the reticulum.

On eight occasions, examinations of the bone marrow were undertaken. Before, as well as after, the splenectomy, an extremely pronounced inhibition and disturbance of the myelopoiesis were observed (barrier after metamyelocytes), as well as of erythropoiesis and a pronounced hyperplasia of the reticulum. After the splenectomy, the condition of the patient improved considerably. The boy has remained well and fairly strong during 9 months. First, the hemoglobin and all the composing elements of the blood rose markedly, retaining their normal values for some time, to disclose again, later, a gradual deterioration. The hemolytic crises, and the predisposition towards bleeding, have disappeared. The most malignant, and remaining, sign manifests itself in a marked immaturity of the white blood picture, and particularly of the myeloid system, which includes forms down to myeloblasts. A temporary improvement after the splenectomy, with the appearance of up to 29 per cent of neutrophil cells during the first half of the year, has been succeeded by a rather considerable deterioration.

The part played by the spleen, in this case, has been very conspicuous, though it concerns, no doubt, a secondary hypersplenia, The prognosis is doubtful (leukemia?). The total disease syndrome may, possibly, be interpreted as a disturbance within the primary blood-forming tissue (reticulosis).

Elias Bengtsson: **The oesophagus ECG of children.**

Examination has been performed of about fifty children, 20 of which were normal cases, the others being myocardites and congenital defects. With a vertical longitudinal axis, a lead from the stomach reflects the potential differences of the left ventricular epicardium. This is even more accentuated with a clockwise rotation. With a horizontal longitudinal axis, the same leads will reflect the right ventricular epicardium, especially at a counter-clockwise rotation. The same applies to a backward rotation of the apex. The more cranially situated a lead, the more the amplitude of the R wave will diminish, at a vertical longitudinal axis, while that of the Q wave will increase. At an auricular level, the auricular wave will, invariably, disclose a fully developed intrinsic deflection. In normal cases, the intrinsic interval has fallen below 0.5 sec. The more cranially situated the lead has been, the more the negative amplitude of the P wave has increased, at the expense of the positive amplitude. In the normal cases, the positive amplitude of the P wave has, in no instance, exceeded 6 mm in leads with a central terminal serving as indifferent electrode, while being somewhat higher when the right arm or a precordial position has been used as indifferent electrode.

Oesophageal leads have produced the most reliable expressions for hypertrophy of the left auricle, particularly in congenital heart disease. In a case of coarctation of the aorta, signs of hypertrophy of the left ventricle were noticeable in the œsophageal leads, but not in other, extremity or thoracic, leads. It has proved possible to follow cases of rheumatic fever for a long time by oesophageal leads, and early signs of auricular hypertrophy have been observed in these leads, but not in any others.

J. Lindahl and T. Johnsson: **Herpangina.**

Accounts are given of 4 cases of herpangina, a syndrome that has not earlier been described in European literature. At the middle of October 1951, a boy, 7 years old, was admitted at the Stockholms Epidemisjukhus for observation of a poliomyelitis. Some days before being admitted, he had fallen ill with severe vomiting, sore throat, abdominal pains and a pyrexia. At his admission, a slight neck-stiffness, a reddened pharynx and reddened tonsils, on the soft palate a spotty enanthema and on the anterior palatal arches some papulovesicular efflorescences, typical of this disease, with a marked redness about them, of a greyish white, measuring about 2 mm. No changes were noted in the anterior parts of the cavity of the mouth. Lumbar puncture without remark. EEG showed a dysrhythmia. After a couple of days afebrile. In the three other cases, the symptoms were similar. Here it was also possible to observe the typical superficial ulcerations that appear as the papulovesicular efflorescences break. In these instances, no sign of meningitic irritation was noted.

The 4 cases occurred sporadically in the course of the month of October, but similar infections have been observed in the environment of the patients. The disease has attracted renewed attention because of its connection with Coxsackie virus. At the Department for Virus Research of Karolinska Institutet in Stockholm, all the 4 cases have been examined with regard to the presence of Coxsackie virus. In 2 of the patients, C-virus was ascertainable in the stools and neutralizing antibodies in the blood against their own strain.

B. Holmgren and S. Kræpelien: **Asthmatic children examined by ECG.**

(Will be published in Acta Paediat.)

G. Berglund, C. G. Engström and G. Tornvall: **Construction of, and experiments with, an oxygen hood for children.**

Proceedings of the Pediatric Society of South Sweden

Meeting at Hälsingborg, September 23, 1951.

N. Lindquist: **Chronic gastric ulcer in infants.**

An infant began to vomit rather severely while still at the maternity hospital and this continued at home. At three months of age the baby was admitted to the Banck Children's Hospital for vomiting, unsatisfactory gain in weight, and crying. Radiographic examination of the stomach showed some irritation around the pylorus but no gross changes. The infant gained weight satisfactorily during his stay in hospital and vomited comparatively little. After discharge from hospital the vomiting again increased and he was readmitted when 4 months old. There was occasionally blood in the vomits and Weber's test on the faeces was positive. Repeated X-ray examinations of the stomach showed a marked stenosis and marked peristalsis but no evidence of hypertrophic pyloric stenosis. As the general condition gradually became worse laparotomy was performed and the pylorus was found to be hypertrophied and a Fredet-Rammstedt operation was carried out. The condition did not improve and the child died when he was 6 months. The autopsy revealed a deep chronic gastric ulcer on the lesser curvature of the stomach, and this was confirmed by microscopic examination.

A. Köiv: **A case of primary tuberculosis of the skin.**

A 6 year old boy with a negative tuberculin test and family history of tuberculosis got a splinter in his right forefinger while at home. A lymphangitis developed in the arm and the boy showed a positive tuberculin reaction. The wound healed slowly and a reddened infiltrated area persisted in the skin; later a swelling of the regional lymphatic glands developed. In addition to the clinical symptoms the diagnosis was verified by a microscopic examination of the skin infiltration and guinea-pig inoculation with the pus from the glandular abscess. Local treatment with dihydrostreptomycin produced good healing. During the following three months no signs of further spreading of the tuberculous infection were observed.

H. Stendahl: **The prognosis for diabetic mothers and their children.**

Report on 227 pregnancies in 154 women with diabetes treated with insulin. Only 50 per cent viable infants were delivered; 10 per cent of these died during the neonatal period and in half of them no cause of death could be found. The age of the mother, the order of the pregnancy, the diabetes duration, severity and effectiveness of control do not seem to have any effect on the prognosis. The prognosis has not improved during the most recent years in spite of the introduction of routine caesarean section and administration of glucose to the new-born.

Ninety-five living children were discharged from the maternity ward. Ten of these died before reaching 10 months of age, mostly from infectious diseases. Within the first year of life another 3 died from infections. Later one child died of a blood disease. None of the deceased children had had any symptoms of diabetes.

The children still living are distributed in different age groups as follows: 2 months to 1 year: 7, 1 to 2 years: 18, 3 to 7 years: 30, 8 to 14 years: 21, and 15 to 20 years: 5, of these 58 have undergone follow-up examinations. First-hand information has been obtained from another 17. The investigation included somatic and psychic history, general condition, and a test for sugar in the urine. One child has diabetes, another was found to have primary tuberculosis, one child is a moron, another is definitely retarded, and one infant is suspected of having a brain lesion. The other children are apparently normal.

N. Lindquist: **Is there any connection between teething and elevated temperature?**

Thirty-two healthy well-tended infants from good homes were subjected to regular temperature control every morning and evening for a long time during the teething period (average period of observation of

227 days; 261 teeth cut). The investigation was carried out at home by selected reliable mothers. Significant difference between normal temperature and the temperature measured during teething days was present in 4 children. The investigation suggests that teething may cause an elevation of temperature in isolated cases but that in the majority of cases the temperature is not affected.

N. Lindquist: **Fifteen years at the Children's Welfare Centre in Hälsingborg.**

A report is given in tables and curves of the range and results of the activity during the period of 1936 to 1950. The mortality in 12,600 supervised children during this period was 0.6 per cent, but in 4,039 non-supervised children it was 2.4 per cent. (The 1st month of life not included.)